(FILE 'HOME' ENTERED AT 08:47:48 ON 09 JUN 2003)

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, ...' ENTERED AT 08:47:57 ON 09 JUN 2003

L1	25780	S	COGNITIVE (W) DISORDER
L2	17585	S	(COGNITIVE AND DISORDER)/AB
L3	871	S	L1 AND L2
L4	0	S	L3 AND (DONEPEZIL OR RIVASTIGMINE OR METRIFONATE OR GALANTA
L5	1369	S	COGNITIVE/AB AND (DONEPEZIL OR RIVASTIGMINE OR METRIFONATE OR
L6	58	S	L5 AND DISORDER/AB
L7	22	DUP REM	L6 (36 DUPLICATES REMOVED)
L8	5	S	L7 AND PD<2000
L9	1746	S	ACETYLCHOLINESTERASE/AB AND COGNITIVE/AB
L10	723	S	L9 AND INHIBITOR/AB
L11	313	S	L10 AND PD<2000
L12	103	DUP REM	L11 (210 DUPLICATES REMOVED)
L13	82	S	L12 AND (DONEPEZIL OR RIVASTIGMINE OR METRIFONATE OR GALANTA
L14	48	S	L12 AND (DONEPEZIL AND RIVASTIGMINE AND METRIFONATE AND GALA
L15	1	S	L12 AND (DONEPEZIL AND RIVASTIGMINE AND METRIFONATE AND GALA

FILE 'USPATFULL' ENTERED AT 09:10:51 ON 09 JUN 2003

L16	9	S	ACETYLCHOLINESTERASE/AB AND COGNITIVE/AB
L17	1	S	L16 AND (DONEPEZIL AND RIVASTIGMINE AND METRIFONATE AND GALA
L18	8	S	L16 NOT L17
L19	5	S	L18 AND (DONEPEZIL AND RIVASTIGMINE AND METRIFONATE AND GALA

L5 ANSWER 1 OF 12 ADISCTI COPYRIGHT (C) 2003 Adis Data Information BV
AN 1999:43941 ADISCTI
DN 807167844
TI The effects of **donepezil** in Alzheimer's disease - results from a multinational trial.
ADIS TITLE: **Donepezil**: therapeutic use.
Alzheimer's disease.
AU Burns A; Rossor M; Hecker J; International Donepezil Study Group; et al.
CS Withington Hospital, Manchester, England; Eisai Inc., Teaneck, New Jersey, USA.
SO Dementia and Geriatric Cognitive Disorders (**Jun 1, 1999**), Vol. 10, pp. 237-244
DT Study
RE Alzheimer's Disease and Cognition Disorders| Neurological Disorders
FS Summary
LA English
WC 875
TI The effects of **donepezil** in Alzheimer's disease - results from a multinational trial.
ADIS TITLE: **Donepezil**: therapeutic use.
Alzheimer's disease.
PD **19990601**
TX . . may play a role in memory impairment. The majority of effective treatments for Alzheimer's disease inhibit the breakdown of acetylcholine. **Donepezil** [**Aricept** sup((R))], a potent **acetylcholinesterase inhibitor**, has been shown to improve **cognitive** and global function in patients with Alzheimer's disease. In addition, **donepezil** is less hepatotoxic than other cholinesterase inhibitors.
This dose-ranging study investigated the efficacy and tolerability of **donepezil** in the treatment of patients with mild to moderately severe Alzheimer's disease.
TX Author Comments:
`Results of this multinational trial confirm previous findings that **donepezil** is well tolerated and efficacious in treating the symptoms of cognitive loss and in improving global functioning in patients with. . . The improvement in IDDD [Interview for Deterioration in Daily living activities in Dementia]-complex tasks also indicates that the benefits of **donepezil** may translate into an effect on complex activities of daily living. Thus, despite variations in local diagnostic and treatment practices, this multinational study demonstrates that **donepezil** therapy is an effective and well tolerated symptomatic treatment for patients with mild to moderately severe AD.'
TX **Donepezil**

Drug/Treatment	Dose	Route	Frequency	Duration
Donepezil (**Aricept** sup((R)))	5 or 10 mg/day	PO	od	24 weeks

TX Patients in the **donepezil** 10 mg/day group received 5 mg/day for the first 7 days, and 10 mg/day for the remainder of the study.. . .
TX Results:

	Placebo	**Donepezil**	
		5 mg/day	10 mg/day
Completion rate (patients)	80%	78%	74%
Improved (patients)	14%	21%	25%

Treatment failures (patients). . . Clinical Dementia Rating scale.

At week 6, compared with placebo, a significant improvement in ADAS-cog

scores was observed in the 2 **donepezil** groups. This improvement was maintained throughout the treatment phase. At weeks 12, 18 and 24, the least- squares mean change in CDR-SB scores was significantly greater in the **donepezil** groups compared with the placebo group ($p < 0.05$). At week 6 and throughout the treatment phase, complex task scores on the Interview for Deterioration in Daily living activities in Dementia (IDDD) were improved in **donepezil**-treated patients compared with placebo. This result was significant for **donepezil** 10 mg/day. After the 6-week placebo washout phase, scores on the ADAS-cog, CIBIC plus, CDR-SB and the IDDD decreased to levels. . .

SIDE Side Effects Table:

Side effects (patients)	Placebo	**Donepezil**	
		5 mg/day	10 mg/day
Adverse events occurring in >= 5% of **donepezil** patients			
Any adverse event	207 (76%)	213 (79%)	234 (86%)
Digestive system events:	65 (24%)	70 (26%) sup(a)	127 (47%).

. . majority of adverse events, excluding cholinergic events (nausea, vomiting and diarrhoea), were not considered to be related to treatment with **donepezil**. No **donepezil** recipients experienced hepatotoxicity.
Overall, 73/818 (9%) patients experienced >= 1 serious adverse event (fatal or life-threatening situations, permanently disabling conditions or incidents requiring or prolonging hospitalisation). Serious events were reported in 25 (9%) placebo recipients, 19 (7%) **donepezil** 5 mg/day recipients and 29 (11%) **donepezil** 10 mg/day recipients. Five patients (2 receiving placebo, 1 receiving **donepezil** 5 mg/day and 2 receiving **donepezil** 10 mg/day) died during the study or <= 1 month after discontinuation of treatment. The deaths were not considered to be related to **donepezil** treatment.

CT Drug Descriptors: **Donepezil**, therapeutic use; Acetylcholinesterase inhibitors, therapeutic use; Antidementias, therapeutic use; Cholinesterase inhibitors, therapeutic use; Enzyme inhibitors, therapeutic use; Neuropsychotherapeutics, therapeutic use;. .

L5 ANSWER 2 OF 12 ADISCTI COPYRIGHT (C) 2003 Adis Data Information BV
AN 1998:53632 ADISCTI
DN 800716429
TI Pharmacokinetic and pharmacodynamic profile of **donepezil** HCl following multiple oral doses.
ADIS TITLE: **Donepezil**: pharmacokinetics.
Pharmacokinetics and pharmacodynamics after multiple doses In volunteers.
AU Rogers S L; Cooper N M; Sukovaty R; Pederson J E; Lee J N; et al.
CS Eisai Inc., Teaneck, New Jersey, USA.
SO British Journal of Clinical Pharmacology (**Nov 1, 1998**), Vol. 46 (Suppl. 1), pp. 7-12
DT Study
RE Alzheimer's Disease and Cognition Disorders| Neurological Disorders
FS Summary
LA English
WC 572
TI Pharmacokinetic and pharmacodynamic profile of **donepezil** HCl following multiple oral doses.
ADIS TITLE: **Donepezil**: pharmacokinetics.
Pharmacokinetics and pharmacodynamics after multiple doses In volunteers.
PD **19981101**
TX Purpose:
Donepezil [**Aricept** sup((R)); Eisai] has recently been

launched worldwide for the treatment of Alzheimer's disease. This drug is an **acetylcholinesterase inhibitor** and has been shown to improve **cognitive** and global functions in patients with dementia.
This study evaluated the pharmacokinetics and pharmacodynamics of **donepezil** after multiple oral doses in volunteers.

TX Author Comments:
`The results of this study demonstrate that once-daily administration of **donepezil** allows achievement of significant AChE [acetylcholinesterase] inhibition throughout the dosing interval, even after the first dose administration. Moreover, repeated administration of oral doses of 1-5 mg of **donepezil** once daily is characterized by predictable pharmacokinetic and pharmacodynamic profiles that are uncomplicated by dose-limiting toxicity.'
`It is suggested that this stable pharmacokinetic and pharmacodynamic profile during repeated administration may simplify the use of **donepezil** in clinical practice.'

TX **Donepezil**

Drug/Treatment	Dose	Route	Frequency	Duration
Donepezil (**Aricept** sup((R)))	1, 3 or 5 mg/day	PO	od	21 days

TX Groups of 8 subjects each received **donepezil** 1, 3 and 5 mg/day according to a sequential design. Within each group, 2 subjects were randomised to receive placebo.

TX Results:

	Donepezil (n = 24)		
	1 mg/day	3 mg/day	5 mg/day

AUC sub(0-24h) (ng x h x ml sup(-1)):
day. . . linear relationships between steady-state AUC sub(0-24h) and C sub(min), as well as C sub(max) on day 1 ($p < 0.001$). **Donepezil** clearance was linear, as demonstrated by significant correlations between dose and steady-state AUC sub(0-24h) and between dose and C sub(ss). . . during the remainder of the study. In the majority of subjects, there was a predictable relationship between acetylcholinesterase inhibition and **donepezil** plasma concentration. Irrespective of treatment duration, there was a strong correlation between AUE and AUC ($p < 0.001$). A mean plasma **donepezil** concentration of 28.7 ng/ml was found to be required to produce EC sub(50) (50% acetylcholinesterase inhibition). The E sub(max) model. . .

SIDE. . . and dizziness) were mild and transient. There were no significant differences in the incidence of adverse events between placebo and **donepezil** recipients. There were no significant changes in vital signs, ECG or laboratory parameters associated with **donepezil** treatment.

CT Drug Descriptors: **Donepezil**, pharmacodynamics; Acetylcholinesterase inhibitors, pharmacodynamics; Antidementias, pharmacodynamics; Cholinesterase inhibitors, pharmacodynamics; Enzyme inhibitors, pharmacodynamics; Neuropsychotherapeutics, pharmacodynamics; Nootropics, pharmacodynamics; **Donepezil**, pharmacokinetics

CT Other Descriptors: Clinical pharmacokinetics; Randomised controlled trials; Clinical trial design

L5 ANSWER 3 OF 12 ADISCTI COPYRIGHT (C) 2003 Adis Data Information BV
AN 1998:53630 ADISCTI
DN 800716428
TI Pharmacokinetic and pharmacodynamic profile of **donepezil** HCl following single oral doses.

ADIS TITLE: **Donepezil**: pharmacokinetics.
Single dose pharmacokinetics and pharmacodynamics
In volunteers.

AU Rogers S L; Friedhoff L T.

CS Eisai Inc., Teaneck, New Jersey, USA.

SO British Journal of Clinical Pharmacology (**Nov 1, 1998**), Vol. 46 (Suppl. 1), pp. 1-6

DT Study

RE Alzheimer's Disease and Cognition Disorders| Neurological Disorders

FS Summary

LA English

WC 396

TI Pharmacokinetic and pharmacodynamic profile of **donepezil** HCl following single oral doses.
ADIS TITLE: **Donepezil**: pharmacokinetics.
Single dose pharmacokinetics and pharmacodynamics
In volunteers.

PD **19981101**

TX Purpose:

Donepezil [**Aricept** sup((R)); Eisai] is an **acetylcholinesterase inhibitor** which has recently been launched worldwide for the improvement of **cognitive** and global functions in patients with Alzheimer's disease.
This study investigated the pharmacokinetic and pharmacodynamic profile of single dose **donepezil** in volunteers.

TX. . . results confirm the findings of earlier studies performed in Japan and suggest that the dose-proportional pharmacokinetic and pharmacodynamic profile of **donepezil** seen in this study will provide the basis for a predictable and specific clinical response in patients with Alzheimer's disease. Its long half-life, which allows once-daily dosing, and its apparent lack of hepatotoxicity at pharmacodynamically effective doses suggest that **donepezil** may be used safely and conveniently in the treatment of Alzheimer's disease.'

TX **Donepezil**

Drug/Treatment	Dose	Route	Duration
Donepezil (**Aricept** sup((R))) single doses	0.3-6.0 mg	PO	

TX Six doses of **donepezil** were tested (0.3, 0.6, 0.9, 2.0, 4.0 and 6.0mg). Groups of 8 subjects were assigned to each dose according to. . .

TX Results:

	Donepezil (n = 48)		
	2mg	4mg	6mg
Single dose pharmacokinetics			
t sub(max) (h)	4.5	4.7	3.2
C sub(max) (ng/ml). . . 33.4%		35.2%	
AUE sub(0-infinity) (% h)	259.0	1488.0	1849.0

AUE = area under the effect curve.
a p < 0.05 vs **donepezil** 2mg.

There was a linear relationship between the AUE sub(0-t) and AUC sub(0-t). The AUE sub(0-t)/AUC sub(0-t) was independent of **donepezil** dose, but a significant positive correlation between acetylcholinesterase inhibition and plasma concentration of **donepezil** was found for the 4 and 6mg dose levels (p < 0.005).

SIDE Side Effects Table:

Donepezil was well tolerated and no abnormalities in ECG, laboratory parameters or vital signs were observed. Reported mild and transient adverse. . . events were nausea, diarrhoea, insomnia, vomiting and fatigue. There were no significant differences in the incidence of adverse events between **donepezil** and placebo recipients.

CT Drug Descriptors: **Donepezil**, pharmacodynamics; Acetylcholinesterase inhibitors, pharmacodynamics; Antidementias, pharmacodynamics; Cholinesterase inhibitors, pharmacodynamics; Enzyme inhibitors, pharmacodynamics; Neuropsychotherapeutics, pharmacodynamics; Nootropics, pharmacodynamics; **Donepezil**, pharmacokinetics

CT Other Descriptors: Clinical pharmacokinetics; Randomised controlled trials; Clinical trial design

L5 ANSWER 4 OF 12 CEN COPYRIGHT 2003 ACS

AN 1998:1565 CEN

TI END RUN AROUND FDA?
Memory enhancer that works like Alzheimer's drugs is being sold via the Internet and will be marketed in stores as `nutraceutical'

AU Borman, Stu

SO Chemical & Engineering News, (**1 Jun 1998**) Vol. 76, No. 22, pp. 45.
CODEN: CENEAR, ISSN: 0009-2347.

PB American Chemical Society

LA English

WC 1801

RN . . .
9001-08-5 (CHOLINESTERASE)
33069-62-4 (TAXOL)
75330-75-5 (LOVASTATIN)
75330-75-5 (MEVACOR)
75330-75-5 (MEVINOLIN)
102518-79-6 (HUPERZINE A)
120014-06-4 (**DONEPEZIL**)

SO Chemical & Engineering News, (**1 Jun 1998**) Vol. 76, No. 22, pp. 45.
CODEN: CENEAR, ISSN: 0009-2347.

TX . . drug for dementia. It acts by inhibiting the enzyme acetylcholinesterase - a mechanism of action shared by Cognex (tacrine) and **Aricept** (**donepezil**), the two major commercial Alzheimer's disease drugs.

Alzheimer's . . . low brain levels of acetylcholine, a neurotransmitter involved in learning and memory. Acetylcholinesterase catalyzes acetylcholine breakdown. Drugs like tacrine and **donepezil** inhibit the enzyme, boosting acetylcholine levels and thus improving the memory and cognition of some Alzheimer's patients. Huperzine, which acts. . .

"This . . . Institute on Aging, in Bethesda, Md. "Huperzine seems to be, from what I understand, about as potent as tacrine or [**donepezil**], and yet it's going to be provided to people without the same kind of clinical trial background as the other. . . What . . . will be readily available without instruction over the counter. It can very well wind up being combined with drugs like **donepezil** by people who think they are going to get enhanced efficacy from a natural product plus a drug," and the. . . Pharmacological, animal-testing, and clinical data from China show that huperzine A is a good **acetylcholinesterase inhibitor**. Xi-Can Tang of the department of pharmacology at Shanghai Institute of Materia Medica reported in a 1996 review article that. . . the dose-limiting hepatotoxicity produced by tacrine. These findings suggest that huperzine A is a promising candidate for palliating therapy of **cognitive** deficits in patients with Alzheimer's disease."

L5 ANSWER 5 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999237304 EMBASE
TI Rivastigmine: An acetylcholinesterase inhibitor for patients with Alzheimer's disease.
AU White C.M.; Dicks R.S.
CS Dr. C.M. White, Clinical Pharmacy, Univ. of Connecticut Sch. of Pharm., Storrs, CT, United States
SO Formulary, (**1999**) 34/6 (493-499).
Refs: 12
ISSN: 1082-801X CODEN: FORMF
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Rivastigmine is an **acetylcholinesterase inhibitor** with FDA approvable status (May 1999) for the treatment of mild to moderate Alzheimer's disease. Rivastigmine raises central nervous system concentrations of acetylcholine. Based on its 10-hour inhibition effect, rivastigmine can be dosed twice daily, even though its terminal half-life in plasma is only 1 hour. Rivastigmine is not thought to have cytochrome P450 drug interactions. In two clinical trials, rivastigmine at 6 to 12 mg/day showed efficacy in slowing deterioration of cognition and in improving behavior and activities of daily living. However, more than 30% of patients receiving rivastigmine in that dose range withdrew from the clinical trials. The most common side effects were gastrointestinal in nature. A phase III trial evaluating rivastigmine's efficacy in preventing progression of patients with mild **cognitive** impairment to Alzheimer's disease is currently being conducted.
SO Formulary, (**1999**) 34/6 (493-499).
Refs: 12
ISSN: 1082-801X CODEN: FORMF
AB Rivastigmine is an **acetylcholinesterase inhibitor** with FDA approvable status (May 1999) for the treatment of mild to moderate Alzheimer's disease. Rivastigmine raises central nervous system. . . side effects were gastrointestinal in nature. A phase III trial evaluating rivastigmine's efficacy in preventing progression of patients with mild **cognitive** impairment to Alzheimer's disease is currently being conducted.
CT Medical Descriptors:
*Alzheimer . . . blind procedure
controlled study
review
*rivastigmine: AE, adverse drug reaction
*rivastigmine: AN, drug analysis
*rivastigmine: DO, drug dose
*rivastigmine: DT, drug therapy
*rivastigmine: PK, pharmacokinetics
*rivastigmine: PD, pharmacology
*tacrine
***donepezil**
cytochrome p450: EC, endogenous compound
RN (rivastigmine) 129101-54-8; (tacrine) 1684-40-8, 3198-41-2, 321-64-2; (**donepezil**) 120011-70-3, 120014-06-4, 142057-77-0; (cytochrome p450) 9035-51-2
CN (1) Cognex; **(2) Aricept**; (3) Ena 713

L5 ANSWER 6 OF 12 COPYRIGHT 2003 Gale Group

AN 1998:69810 NLDB

TI Metrifonate Shows Efficacy In Behavior Dysfunction
SO Marketletter, (**16 Mar 1998**) .
ISSN: 0951-3175.
PB Marketletter Publications Ltd. (UK)
DT Newsletter
LA English
WC 391
SO Marketletter, (**16 Mar 1998**) .
ISSN: 0951-3175.
TX Bayer's **acetylcholinesterase inhibitor** metrifonate may also have potential in the psychiatric and behavioral symptoms of Alzheimer's disease as well as improving **cognitive** function, according to data presented at the American Association of Geriatric Psychiatry. In the trial, 408 patients were randomized to. . .

Previously-released . . . Help Market Position? Once launched, the new data may help the company to position metrifonate ahead of the competition, Eisai/Pfizer's **Aricept** (**donepezil**) and Novartis' Exelon (rivastigmin), as this is the first time that an AChE inhibitor has been shown to benefit behavioral. . .

L5 ANSWER 7 OF 12 COPYRIGHT 2003 Gale Group

AN 97:370207 NLDB
TI Efficacy And Safety Of **Aricept** Questioned
SO Marketletter, (**3 Nov 1997**) .
ISSN: 0951-3175.
PB Marketletter Publications Ltd. (UK)
DT Newsletter
LA English
WC 278
TI Efficacy And Safety Of **Aricept** Questioned
SO Marketletter, (**3 Nov 1997**) .
ISSN: 0951-3175.
TX Eisai/Pfizer's acetylcholinesterase inhibitor **Aricept** (**donepezil**) was licensed in the UK earlier this year for the symptomatic treatment of mild-to-moderately severe Alzheimer's dementia (Marketletter March 3).

However, . . . has been questioned in a report published in the Drugs and Therapeutics Bulletin (October issue). The article says that as **donepezil** increases cholinergic transmission, then its therapeutic benefits "must depend on the presence of functioning cholinergic neurones." In that case, the therapeutic effects of an **acetylcholinesterase inhibitor** must diminish during the course of the disease as the number of cholinergic neurones decreases. Data Not Fully Published The. . . patients with mild-to-moderately-severe Alzheimer's disease, has been published in full; data from an open-label study looking at long-term treatment with **donepezil** has been published in abstract form only, as have the results from a Phase III, 450-patient trial. In the published trial, patients were administered either placebo or 1mg, 3mg or 5mg of **donepezil** every day for 12 weeks. Treatment with 3mg or 5mg of **donepezil** was found to significantly improve ADAS-Cog **cognitive** subscale scores compared to placebo. However, there was no difference between the treated and placebo groups in Clinical Global Impression. . . quality-of-life scores, the report adds. It concludes that based on the published evidence available, it cannot recommend the use of **donepezil**, and adds that in its view "it is not acceptable to ask doctors to make decisions on the basis of. . .

L5 ANSWER 8 OF 12 COPYRIGHT 2003 Gale Group

AN 97:224284 NLDB

TI Nicotine's Good Side: Treating Brain Diseases-Part 3
SO Genesis Report-Rx, (**1 Apr 1996**) Vol. 5, No. 3.
ISSN: 1061-2270.
PB Genesis Group Associates, Inc
DT Newsletter
LA English
WC 3200
SO Genesis Report-Rx, (**1 Apr 1996**) Vol. 5, No. 3.
ISSN: 1061-2270.
TX **Aricept** (**donepezil** A double-blind,
placebo-controlled trial

inhibitor for once-daily **Aricept** dosing over the

Interleukin-2 (IL-2) **the**
DAB3981L-2 clinical trial and agreed

L5 ANSWER 9 OF 12 PHARMAML COPYRIGHT 2003 MARKETLETTER
AN 1640803 PHARMAML
TI Metrifonate Shows Efficacy In Behavior Dysfunction
SO Marketletter March 11, 1998
DT Newsletter
WC 382
PD **19980311**
TX Bayer's **acetylcholinesterase inhibitor** metrifonate
may also have potential in the psychiatric and behavioral symptoms of
Alzheimer's disease as well as improving **cognitive** function,
according to data presented at the American Association of Geriatric
Psychiatry.
Help Market Position? Once launched, the new data may help the company to
position metrifonate ahead of the competition, Eisai/Pfizer's
Aricept (**donepezil**) and Novartis' Exelon (rivastigmin),
as this is the first time that an AChE inhibitor has been shown to
benefit behavioral. . .
Meantime, research presented at the Annual Symposium of the American
Medical Directors Association has shown that slowing the progression of
cognitive symptoms in AD will substantially delay the requirement
for nursing care in these patients. Bruce Kinosian, lead investigator,
said that "assuming that a new therapy for AD maintains a slowing of the
progression of **cognitive** losses, the probability of patients
being institutionalized would be reduced by 5% over a five-year period."

L5 ANSWER 10 OF 12 PHARMAML COPYRIGHT 2003 MARKETLETTER
AN 1638981 PHARMAML
TI Efficacy And Safety Of **Aricept** Questioned
SO Marketletter October 29, 1997
DT Newsletter
WC 277
PD **19971029**
TI Efficacy And Safety Of **Aricept** Questioned
TX Eisai/Pfizer's **acetylcholinesterase inhibitor**
Aricept (**donepezil**) was licensed in the UK earlier this
year for the symptomatic treatment of mild-to-moderately severe
Alzheimer's dementia (Marketletter March 3).. . .
The article says that as **donepezil** increases cholinergic
transmission, then its therapeutic benefits "must depend on the presence
of functioning cholinergic neurones." In that case, the therapeutic
effects of an **acetylcholinesterase inhibitor** must
diminish during the course of the disease as the number of cholinergic
neurones decreases.
. . . patients with mild-to-moderately-severe Alzheimer's disease, has
been published in full; data from an open-label study looking at
long-term treatment with **donepezil** has been published in
abstract form only, as have the results from a Phase III, 450-patient

trial.
In the published trial, patients were administered either placebo or 1mg, 3mg or 5mg of **donepezil** every day for 12 weeks.
Treatment with 3mg or 5mg of **donepezil** was found to significantly improve ADAS-Cog **cognitive** subscale scores compared to placebo. However, there was no difference between the treated and placebo groups in Clinical Global Impression. . .
It concludes that based on the published evidence available, it cannot recommend the use of **donepezil**, and adds that in its view "it is not acceptable to ask doctors to make decisions on the basis of. . .

L5 ANSWER 11 OF 12 PHARMAML COPYRIGHT 2003 MARKETLETTER
AN 1634394 PHARMAML
TI Pfizer Drops Tenidap For RA, But OA Still An Option
SO Marketletter October 7, 1996
DT Newsletter
WC 555
PD **19961007**
TX Pfizer's **Donepezil** Now Approvable In USA Meantime, there was better news for Pfizer with the issuance of an approvable letter in the USA for **Aricept** (**donepezil** hydrochloride; E2020), an **acetylcholinesterase inhibitor** licensed from Eisai of Japan, which is indicated for the treatment of mild-to-moderate symptoms in Alzheimer's disease.
According to the results of clinical trials, **donepezil** can improve the **cognitive** function of AD patients in four of five tests, and shows the ability to prevent deterioration of memory and daily. . . two years or longer, without patients suffering significant adverse effects. It has not been shown to reduce progression. Most importantly, **donepezil** does not appear to cause the hepatotoxicity which limits the use of Warner-Lambert's **acetylcholinesterase inhibitor** Cognex (tacrine), the only approved drug for AD.

L5 ANSWER 12 OF 12 PHARMAML COPYRIGHT 2003 MARKETLETTER
AN 1632497 PHARMAML
TI Eisai Files For **Aricept** In USA; Phase III Data
SO Marketletter April 8, 1996
DT Newsletter
WC 547
PD **19960408**
TI Eisai Files For **Aricept** In USA; Phase III Data
TX Eisai America, a subsidiary of Eisai of Japan, has filed a New Drug Application in the USA for **Aricept** (**donepezil** HCl; formerly E2020), its new **acetylcholinesterase inhibitor** for the treatment of Alzheimer's dementia.
If approved, **Aricept** will be comarketed by Eisai and partner Pfizer, under the terms of the strategic alliance signed by the two companies in November 1994. **Aricept** is the lead compound in this alliance, which focuses on the development of new drugs for Alzheimer's disease and other **cognitive** disorders.
The results of Phase III trials of **Aricept** were presented at the American College of Neurology meeting at the end of March. These data showed that once-daily administration of **Aricept** produced a statistically significant improvement in cognition and daily functioning scores for patients with mild-to-moderate disease. The drug was well-tolerated. . .
. . . Phase III study presented at the AAN enrolled 450 patients, with 150 patients randomized to one of three treatment arms; **donepezil** 5mg/day, **donepezil** 10mg/day or placebo. The trial was conducted over a 30-week period, and the primary endpoints were performance on the Alzheimer's Disease Assessment Scale-**cognitive** subscale (ADAS-cog) and the Clinician's Interview-based Impression of Change, with input from the patient carer (CIBIC-Plus).

Top-Line Data The researchers found that **donepezil** was well-tolerated over the course of the study. In addition, statistically significant improvements were observed with both the 5mg and 10mg **donepezil** groups compared to placebo on the ADAS-cog and the CIBIC-Plus scales. The drug reduced the number of treatment failures by. . .

Overall, around 25% of Alzheimer's patients who received **donepezil** had meaningful improvements in memory and other **cognitive** skills, evidenced by a seven-point increase in the test scale. Furthermore, 81% of the **donepezil** patients experienced either no decline in **cognitive** ability or an improvement.

Ranking the daily functioning scores, it was found that 56% of those in the placebo group worsened by the end of the study, compared to 32% on **donepezil**.

. . . submitted to the Food and Drug Administration, said Eisai America. The dossier also includes data on patients who have received **Aricept** for over three years and supports the long-term safety of the drug.

Comparing **Aricept** to the only approved drug for Alzheimer's, Warner-Lambert's Cognex (tacrine), Zaven Katchaturian, director of the US Alzheimer's Association's Ronald and Nancy Reagan Research Institute, said that the data suggests that the two drugs offer comparable efficacy. Unlike Cognex, however, **Aricept** caused no serious side effects, and particularly no liver toxicity.

Duration Of Benefit Eisai now hopes to demonstrate that **Aricept** can provide sustained effects on **cognitive** function - Cognex' activity seems to wane after about a year. The company said that preliminary data on 50 patients indicated that **donepezil** may be effective for up to two years, but this will require confirmation in larger studies. It also remains to. . .

Aricept remains in Phase III testing in Europe, Canada, Australia, New Zealand and South Africa and will enter Phase III trials. . .

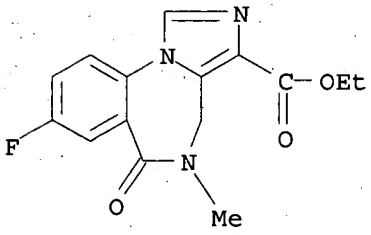
=>

(FILE 'HOME' ENTERED AT 09:51:30 ON 09 JUN 2003)

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, ...' ENTERED AT 09:51:35 ON 09 JUN 2003

L1	643	S COGNITIVE (P) (ACETYLCHOLINESTERASE (W) INHIBITOR)
L2	294	DUP REM L1 (349 DUPLICATES REMOVED)
L3	126	S L2 AND PD<2000
L4	89	S L3 AND (DONEPEZIL OR RIVASTIGMINE OR METRIFONATE OR GALANTA
L5	12	S L3 AND (DONEPEZIL AND ARICEPT)
L6	0	S L5 AND (COGNITIVE (W) DISORDER)
L7	1	S L5 AND (COGNITIVE (W) DISEASE)
L8	0	S L5 AND (COGNITIVE (W) DYSFUNCTION)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 78755-81-4 REGISTRY
CN 4H-Imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid,
8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Anexate
CN Flumazenil
CN Flumazepil
CN Flumenazil
CN Lanexat
CN Mazicon
CN **Ro 15-1788**
CN Ro 15-1788/000
CN Ro 151788
CN Ro 1722
CN Ro 41-8157
CN Romazicon
FS 3D CONCORD
MF C15 H14 F N3 O3
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1341 REFERENCES IN FILE CA (1957 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1344 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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L4   ANSWER 1 OF 3  USPATFULL
AN     2002:61284  USPATFULL
TI     Oxo-imidazopyridine-carboxamides
IN     Cai, Guolin, Thousand Oaks, CA, UNITED STATES
       Albaugh, Pamela A., Carmel, IN, UNITED STATES
       Shaw, Kenneth, Weston, CT, UNITED STATES
PI     US 2002035120      A1   20020321
AI     US 2001-864846     A1   20010524 (9)
PRAI   US 2000-209855P     20000526 (60)
DT     Utility
FS     APPLICATION
LREP   Steven J. Sarussi, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300
       S. Wacker Drive, Chicago, IL, 60606
CLMN   Number of Claims: 65
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 1499
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 2 OF 3  USPATFULL
AN     2002:55037  USPATFULL
TI     2-Substituted imidazo[1,2-A]pyridine derivatives
IN     Cai, Guolin, Thousand Oaks, CA, UNITED STATES
       Shaw, Kenneth, Weston, CT, UNITED STATES
PI     US 2002032200      A1   20020314
       US 6552037         B2   20030422
AI     US 2001-897837     A1   20010629 (9)
PRAI   US 2000-215646P     20000630 (60)
DT     Utility
FS     APPLICATION
LREP   Steven J. Sarussi, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300
       S. Wacker Drive, Chicago, IL, 60606
CLMN   Number of Claims: 47
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 1541
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4   ANSWER 3 OF 3  USPATFULL
AN     2002:32588  USPATFULL
TI     Imidazoloisoquinolines
IN     Cai, Guolin, Thousand Oaks, CA, UNITED STATES
       Shaw, Kenneth, Weston, CT, UNITED STATES
PA     Neurogen Corporation (U.S. corporation)
PI     US 2002019410      A1   20020214
       US 6528649         B2   20030304
AI     US 2001-867304     A1   20010529 (9)
PRAI   US 2000-207796P     20000530 (60)
DT     Utility
FS     APPLICATION
LREP   Steven J. Sarussi, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300
       S. Wacker Drive, Chicago, IL, 60606
CLMN   Number of Claims: 45
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 1389
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d l4 1-3 kwic

L4   ANSWER 1 OF 3  USPATFULL
AB     A, B, C, E, F, and G are substituents as defined herein, which compounds
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bind to the benzodiazepine site of **GABA**.sub.A receptors and are therefore useful in treatment of central nervous system (CNS) diseases.

SUMM [0003] This invention relates to oxo-imidazopyridine-carboxamides that bind with high selectively and high affinity to the benzodiazepine site of **GABA**.sub.A receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment. . .

SUMM [0005] The **GABA**.sub.A receptor super-family represents one of the classes of receptors through which the major inhibitory neurotransmitter, .gamma.-aminobutyric acid, or **GABA**, acts. Widely, although unequally, distributed through the mammalian brain, **GABA** mediates many of its actions through a complex of proteins called the **GABA**.sub.A receptor, which causes alteration in chloride conductance and membrane polarization. In addition to being the site of neurotransmitter action, a number of drugs including the anxiolytic and sedating benzodiazepines bind to this receptor. The **GABA**.sub.A receptor comprises a chloride channel that generally, but not invariably, opens in response to **GABA**, allowing chloride to enter the cell. This, in turn, effects a slowing of neuronal activity through hyper-polarization of the cell. . .

SUMM [0006] **GABA**.sub.A receptors are composed of five protein subunits. A number of cDNAs for these **GABA**.sub.A receptor subunits have been cloned and their primary structures determined. While these subunits share a basic motif of 4 membrane-spanning. . . them into several groups. To date at least 6.alpha., 3.beta., 3.gamma., 1.epsilon., 1.delta. and 2.rho. subunits have been identified. Native **GABA**.sub.A receptors are typically composed of 2.alpha., 2.beta., and 1.gamma. subunits (Pritchett & Seeburg Science 1989; 245:1389-1392, and Knight et. al.,. . .

SUMM [0007] The **GABA**.sub.A receptor binding sites for **GABA** (2 per receptor complex) are formed by amino acids from the .alpha. and .beta. subunits. Amino acids from the .alpha.. . . 1 benzodiazepine site per receptor. Benzodiazepines exert their pharmacological actions by interacting with the benzodiazepine binding sites associated with the **GABA**.sub.A receptor. In addition to the benzodiazepine site (sometimes referred to as the benzodiazepine or BDZ receptor), the **GABA**.sub.A receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site, and a barbiturate site. The benzodiazepine site of the **GABA**.sub.A receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for other classes of drugs that bind to the receptor or for **GABA** (see, e.g., Cooper, et al., The Biochemical Basis of Neuropharmacology, 6.sup.th ed., 1991, pp. 145-148, Oxford University Press, New York).

SUMM [0008] In a classic allosteric mechanism, the binding of a drug to the benzodiazepine site increases the affinity of the **GABA** receptor for **GABA**. Benzodiazepines and related drugs that enhance the ability of **GABA** to open **GABA**.sub.A receptor channels are known as agonists or partial agonists depending on the level of **GABA** enhancement. Other classes of drugs, such as .beta.-carboline derivatives, that occupy the same site and negatively modulate the action of **GABA** are called inverse agonists. A third class of compounds exists. These compounds occupy the same site as both the agonists and inverse agonists and yet have little or no effect on **GABA** activity. These compounds will, however, block the action of agonists or inverse agonists and are thus referred to as **GABA**.sub.A receptor antagonists.

SUMM . . . enjoyed long pharmaceutical use as anxiolytics, these compounds are known to exhibit a number of unwanted side effects. These include **cognitive** impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

SUMM [0010] **GABA**.sub.A selective ligands also act to potentiate the effects of certain other CNS active compounds. For example, there is

evidence that selective serotonin reuptake inhibitors (SSRIs) display greater antidepressant activity when used in combination with **GABA**.sub.A selective ligands than when used alone.

SUMM [0011] This invention provides oxo-imidazopyridine-carboxamide derivatives that bind with high affinity and high selectivity to the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A receptors. Compounds of the invention bind, preferably with high selectivity and affinity, to **GABA**.sub.A receptors and thereby act as agonists, antagonists or inverse agonists of such receptors. As such, they are useful in the. . .

SUMM [0012] The compounds of the invention bind with high selectivity and high affinity to the benzodiazepine site of **GABA**.sub.A receptors.

SUMM . . . In another, aspect this invention relates to the use of compounds of Formula I as probes for the localization of **GABA** .sub.A receptors in tissue sections. Such probes may be used in vitro (e.g., in binding assays) or in vivo (e.g., in. . .

DETD [0136] The compounds of the invention interact with a **GABA** binding site, the benzodiazepine (BDZ) receptor, as shown in the examples.

DETD [0137] This invention provides oxo-imidazopyridine carboxamides that bind, preferably with high affinity, to the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A receptors. Preferred compounds are those that show high selectivity for the benzodiazepine site of **GABAa** receptors.

DETD . . . The compounds of Formula I and their salts are suitable for the diagnosis and treatment of anxiety, depression, memory impairment, **Alzheimer**'s dementia, Down Syndrome, sleep, **cognitive** and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness, both in human and non-human animals including. . .

DETD [0147] cognition impairment, **Alzheimer**'s disease, Parkinson's disease, mild **cognitive** impairment (MCI), age-related **cognitive** decline (ARCD), stroke, traumatic brain injury, AIDS associate dementia, dementia associated with depression, anxiety or psychosis

DETD . . . that act as inverse agonists at an .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtype or .alpha..sub.1.beta..sub.2.gamma..sub.2 and .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtypes are useful in treating **cognitive** disorders including those resulting from Down Syndrome, neurodegenerative diseases such as **Alzheimer**'s disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at a .alpha..sub.1.beta..sub.2.gamma..sub.2 receptor. . .

DETD . . . antagonists or corticotropin releasing factor receptor (CRF.sub.1) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as **Alzheimer**'s dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. In a preferred embodiment, the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering an effective amount of a **GABA** agonist compound of the invention in combination with an SSRI.

DETD . . . or Le, et al., Alcohol and Alcoholism (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the **GABA**.sub.A receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methyloxy-1,2,4-triazolo [3,4-a]phthalzine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos.. . . see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of **GABA**.sub.A receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

DETD [0152] The present invention also pertains to methods of inhibiting the

binding of benzodiazepine compounds, such as Ro15-1788, to **GABA** .sub.A receptors which methods involve contacting a compound of the invention with cells expressing **GABA**.sub.A receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding to **GABA**.sub.A receptors in vitro. This method includes inhibiting the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vitro. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the **GABA**.sub.A receptor may be readily determined via an **GABA**.sub.A receptor binding assay, such as the assay described in Example 9. The **GABA**.sub.A receptors used to determine in vitro binding may be obtained from a variety of sources, such as, for example, from preparations of rat cortex or from cells expressing cloned human **GABA**.sub.A receptors.

DETD [0153] The present invention also pertains to methods for altering the signal-transducing activity, particulary the chloride ion conductance of **GABA**.sub.A receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of **GABA**.sub.A receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of **GABA**.sub.A receptors in vitro. The amount of a compound that would be sufficient to alter the signal-transducing activity of **GABA**.sub.A receptors may be determined via a **GABA**.sub.A receptor signal transduction assay, such as the assay described in Example 10.

DETD [0154] The **GABAreceptor** ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the **GABA**.sub.A receptor.

DETD [0155] Labeled derivatives the **GABA**.sub.A receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single. . .

DETD [0156] Additionally this invention relates to the use of compounds of Formula I as probes for the localization of **GABA**.sub.A receptors, e.g., in tissue sections.

DETD . . . most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or **cognitive** impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a. . .

DETD [0175] The present invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to **GABA**.sub.A receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or **cognitive** impairment by **GABA**.sub.A receptor modulation. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one **GABA**.sub.A receptor modulator as described herein and instructions (e.g., labeling) indicating the contained **GABA** .sub.A receptor ligand is to be used for treating a disorder responsive to **GABA**.sub.A receptor modulation in the patient.

DETD [0201] The following assay is a standard **GABAa** receptor binding assay. The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the **GABA**.sub.A receptor is shown using the binding assay described by Thomas and Tallman (J. Bio. Chem. 1981; 156:9838-9842, and J. Neurosci.. . .

DETD . . . compound of the invention act as an agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the **GABA** .sub.A receptor.

DETD . . . subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1 .mu.M

GABA is applied.

DETD [0208] Compounds are evaluated against a **GABA** concentration that evokes <10% of the maximal evokable **GABA** current (e.g. 1 .mu.M-9.mu.M). Each oocyte is exposed to increasing concentrations of a compound being evaluated (test compound) in order. . . evaluate a concentration/effect relationship. Test compound efficacy is calculated as a percent-change in current amplitude: 100*((Ic/I)-1), where Ic is the **GABA** evoked current amplitude observed in the presence of test compound and I is the **GABA** evoked current amplitude observed in the absence of the test compound.

DETD . . . of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied test compound, the oocyte is exposed to **GABA**+1 .mu.M RO15-1788, followed by exposure to **GABA**+1 .mu.M RO15-1788+test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in. . .

CLM What is claimed is:

42. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound or salt according to claim. . . the cell, wherein a detectable alteration of the electrophysiology of the cell indicates an alteration of the signal-transducing activity of **GABA**.sub.A receptors.

44. The method of claim 42 wherein the cell is recombinantly expressing a heterologous **GABA**.sub.A receptor and the alteration of the electrophysiology of the cell is detected by intracellular recording or patch clamp recording.

47. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, the method comprising exposing cells expressing **GABA**.sub.A receptors to a compound or salt according to claim 1 at a concentration sufficient to inhibit RO15-1788 binding in vitro to cells expressing a human **GABAA** receptor.

48. A method for the treatment of anxiety, depression, a sleep disorder, or **Alzheimer**'s dementia comprising administering an effective amount of a compound or salt of claim 1 to a patient in need thereof.

. . .

49. A method for demonstrating the presence of **GABA**.sub.A receptors in cell or tissue samples, said method comprising: (a) preparing a plurality of matched cell or tissue samples, (b) preparing at least one control sample by contacting (under conditions that permit binding of RO15-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . first measured concentration, (c) preparing at least one experimental sample by contacting (under conditions that permit binding of RO15-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of **GABA**.sub.A receptors in that experimental sample.

. . . and further comprising indicia comprising at least one of: instructions for using the composition to treat a patient suffering from **Alzheimer**'s dementia or instructions for using the composition to enhance cognition in a patient.

. . . use of a compound or salt according to claim 1 for the treatment of anxiety, depression, a sleep disorder, or **Alzheimer**'s dementia.

IT **78755-81-4**, RO15-1788

(prepn. of 5-oxo-imidazo[1,2-a]pyridine-3-carboxamides as GABA brain receptor ligands)

L4 ANSWER 2 OF 3 USPATFULL

AB . . . and W are defined herein, which compounds bind with high selectivity and high affinity to the benzodiazepine site of the **GABA**.sub.A receptors and are therefore useful in the treatment of certain central nervous system (CNS) diseases and as probes for the localization of **GABA**.sub.A receptors in tissue samples.

SUMM . . . derivatives and more specifically to such compounds that bind with high selectivity and high affinity to the benzodiazepine site of **GABA**.sub.A receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment. . .

SUMM [0003] The **GABA**.sub.A receptor superfamily represents one of the classes of receptors through which the major inhibitory neurotransmitter, .gamma.-aminobutyric acid, or **GABA**, acts. Widely, although unequally, distributed through the mammalian brain, **GABA** mediates many of its actions through a complex of proteins called the **GABA**.sub.A receptor, which causes alteration in chloride conductance and membrane polarization.

SUMM [0004] A number of cDNAs for **GABA**.sub.A receptor subunits have been characterized. To date at least 6.alpha., 3.beta., 3.gamma., 1.epsilon., 1.delta. and 2.rho. subunits have been identified. It is generally accepted that native **GABA**.sub.A receptors are typically composed of 2.alpha., 2.beta., and 1.gamma. subunits. Evidence such as message distribution, genome localization and biochemical study. . .

SUMM [0005] Benzodiazepines exert their pharmacological actions by interacting with the benzodiazepine binding sites associated with the **GABA**.sub.A receptor. In addition to the benzodiazepine site, the **GABA**.sub.A receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site, and the barbiturate site. The benzodiazepine site of the **GABA**.sub.A receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for **GABA** or for other classes of drugs that bind to the receptor (see, e.g., Cooper, et al., The Biochemical Basis of. . . 145-148, Oxford University Press, New York). Early electrophysiological studies indicated that a major action of the benzodiazepines was enhancement of **GABAergic** inhibition. Compounds that selectively bind to the benzodiazepine site and enhance the ability of **GABA** to open **GABA**.sub.A receptor channels are agonists of **GABA** receptors. Other compounds that interact with the same site but negatively modulate the action of **GABA** are called inverse agonists. Compounds belonging to a third class bind selectively to the benzodiazepine site and yet have little or no effect on **GABA** activity, but can block the action of **GABA**.sub.A receptor agonists or inverse agonists that act at this site. These compounds are referred to as antagonists.

SUMM . . . long history of pharmaceutical use as anxiolytics, these compounds often exhibit a number of unwanted side effects. These may include **cognitive** impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

SUMM [0007] **GABA**.sub.A selective ligands may also act to potentiate the effects of certain other CNS active compounds. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) may show greater antidepressant activity when used in combination with **GABA**.sub.A selective ligands than when used alone.

SUMM . . . are certain novel compounds, particularly 2-phenylimidazo[1,2-a]pyridine derivatives that bind to cell surface receptors. Preferred compounds of the invention bind to **GABA** receptors, in particular these compounds possess affinity for the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A

receptors. Also preferred are compounds that exhibit high selectivity to the benzodiazepine site of the **GABA**.sub.A receptor. These compounds are therefore considered to be of potential use in the treatment of a broad array of diseases or disorders in patients, which are characterized by modulation of **GABA**.sub.A receptors.

SUMM [0010] Such diseases or disorders include, but are not limited to depression, anxiety, sleep disorders, **cognitive** disorders, low alertness, psychosis, obesity, pain, Parkinson's disease, **Alzheimer**'s disease, neurodegenerative diseases, movement disorders, Down's syndrome, and benzodiazepine overdoses.

SUMM [0014] Additionally this invention relates to the use of the compounds of the invention as probes for the localization of **GABA**.sub.A receptors in tissue sections.

SUMM [0123] This invention relates to 2-phenylimidazo[1,2-a]pyridine derivatives that bind with high affinity and high selectivity to the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A receptors.

SUMM [0130] Cognition impairment: cognition impairment, **Alzheimer**'s disease, Parkinson's disease, mild **cognitive** impairment (MCI), age-related **cognitive** decline (ARCD), stroke, traumatic brain injury, AIDS associate dementia, dementia associated with depression, anxiety or psychosis.

SUMM . . . that act as inverse agonists at the .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtype or .alpha..sub.1.beta..sub.2.gamma..sub.2 and .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtypes are useful in treating **cognitive** disorders including those resulting from Down Syndrome, neurodegenerative diseases such as **Alzheimer**'s disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at the .alpha..sub.1.beta..sub.2.gamma..sub.2 receptor. . .

SUMM . . . antagonists or corticotropin releasing factor receptor (CRF.sub.1) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as **Alzheimer**'s dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Particularly the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering a therapeutically effective amount of a **GABA** agonist compound of the invention in combination with an SSRI.

SUMM . . . or Le, et al., Alcohol and Alcoholism (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the **GABA**.sub.A receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methyloxy-1,2,4-triazolo [3,4-a]phthalzine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos.. . . see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of **GABA**.sub.A receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

SUMM [0134] This invention also pertains to methods of inhibiting the binding of benzodiazepine compounds, such as Ro15-1788, to the **GABA**.sub.A receptors which methods involve contacting a compound of the invention with cells expressing **GABA**.sub.A receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding to **GABA**.sub.A receptors in vitro. This method includes inhibiting the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vitro. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the **GABA**.sub.A receptor may be readily determined via a **GABA**.sub.A receptor binding assay, such as the assay described in Example 6.

The **GABA**.sub.A receptors used to determine in vitro binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human **GABA**.sub.A receptors.

SUMM [0135] The invention also pertains to methods for altering the signal-transducing activity, particularly the chloride ion conductance, of **GABA**.sub.A receptors, said method comprising exposing cells expressing such receptors to a therapeutically effective amount of a compound of the invention. This method includes altering the signal-transducing activity of **GABA**.sub.A receptor s in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of **GABA** .sub.A receptors in vitro. The amount of a compound that would be sufficient to alter the signal-transducing activity of **GABA** .sub.A receptors may be determined via a **GABA**.sub.A receptor signal transduction assay, such as the assay described in Example 7.

SUMM [0136] The **GABA**.sub.A receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the **GABA**.sub.A receptor.

SUMM [0137] Labeled derivatives the **GABA**.sub.A receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single. . .

SUMM [0138] More particularly compounds of the invention may be used for demonstrating the presence of **GABA**.sub.A receptors in cell or tissue samples. This may be done by preparing a plurality of matched cell or tissue samples,. . . prepared as a control sample. The experimental sample is prepared by contacting (under conditions that permit binding of RO15-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples that has not previously. . .

SUMM . . . in the at least one washed experimental sample than is detected in any of control samples demonstrates the presence of **GABA** .sub.A receptors in that experimental sample.

SUMM . . . most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or **cognitive** impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a. . .

SUMM [0179] The invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to **GABA**.sub.A receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or **cognitive** impairment by **GABA**.sub.A receptor modulation. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one **GABA**.sub.A receptor modulator as described supra and instructions (e.g., labeling) indicating the contained **GABA** .sub.A receptor ligand is to be used for treating a disorder responsive to **GABA**.sub.A receptor modulation in the patient.

DETD [0202] The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the **GABA**.sub.A receptor is confirmed using the binding assay described in Thomas and Tallman (J. Bio. Chem. 1981; 156:9838-9842, and J. Neurosci.. . .

DETD . . . compound of the invention act as an agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the **GABA** .sub.A receptor.

DETD . . . subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1 .mu.M **GABA** is applied.

DETD [0209] Compounds are evaluated against a **GABA** concentration that evokes <10% of the maximal evokable **GABA** current (e.g. 1 .mu.M -9 .mu.M). Each oocyte is exposed to increasing concentrations of compound in order to evaluate a concentration/effect relationship. Compound efficacy is calculated as a percent-change in current amplitude: 100*((Ic/I)-1), where Ic is the **GABA** evoked current

amplitude observed in the presence of test compound and I is the **GABA** evoked current amplitude observed in the absence of the test compound.

DETD . . . completion of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied compound, the oocyte is exposed to **GABA**+1 .mu.M RO15-1788, followed by exposure to **GABA**+1 .mu.M RO15-1788+ test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed. . .

CLM What is claimed is:

26. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound or salt according to claim. . . the cell, wherein a detectable alteration of the electrophysiology of the cell indicates an alteration of the signal-transducing activity of **GABA**.sub.A receptors.

27. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound or salt according to claim 1 at a concentration sufficient to detectably alter the chloride conductance in vitro of cell expressing **GABA** .sub.A receptors.

29. The method of claim 28 wherein the cell is recombinantly expressing a heterologous **GABA**.sub.A receptor and the alteration of the electrophysiology of the cell is detected by intracellular recording or patch clamp recording.

32. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, the method comprising exposing cells expressing **GABA**.sub.A receptors to a compound or salt according to claim 1 at a concentration sufficient to inhibit RO15-1788 binding in vitro to cells expressing a human **GABA**.sub.A receptor.

33. A method for the treatment of anxiety, depression, a sleep disorder, or **Alzheimer**'s dementia comprising administering an effective amount of a compound or salt of claim 1 to a patient in need thereof. . . .

34. A method for demonstrating the presence of **GABA**.sub.A receptors in cell or tissue samples, said method comprising preparing a plurality of matched cell or tissue samples, preparing at least one control sample by contacting (under conditions that permit binding of RO15-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . said first measured concentration, preparing at least one experimental sample by contacting (under conditions that permit binding of RO15-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of **GABA**.sub.A receptors in that experimental sample.

. . . and further comprising indicia comprising at least one of: instructions for using the composition to treat a patient suffering from **Alzheimer**'s dementia or instructions for using the composition to enhance cognition in a patient.

IT **78755-81-4**, RO15-1788
(prepn. of 2-substituted imidazo[1,2-a]pyridines with high selectivity and high affinity to the benzodiazepine site of the GABAA receptors)

L4 ANSWER 3 OF 3 USPATFULL

AB . . . and X are defined herein, which compounds bind with high selectivity and high affinity to the benzodiazepine site of the **GABA**.sub.A receptors and are therefore useful in the treatment of certain central nervous system (CNS) diseases and as probes for the localization of **GABA**.sub.A receptors in tissue samples.

SUMM . . . imdazoloisoquinolines and more specifically to such compounds that bind with high selectivity and high affinity to the benzodiazepine site of **GABA**.sub.A receptors. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment. . .

SUMM [0005] The **GABA**.sub.A receptor superfamily represents one of the classes of receptors through which the major inhibitory neurotransmitter, .gamma.-aminobutyric acid, or **GABA**, acts. Widely, although unequally, distributed through the mammalian brain, **GABA** mediates many of its actions through a complex of proteins called the **GABA**.sub.A receptor, which causes alteration in chloride conductance and membrane polarization.

SUMM [0006] A number of cDNAs for **GABA**.sub.A receptor subunits have been characterized. To date at least 6.alpha., 3.beta., 3.gamma., 1.epsilon., 1.delta. and 2.rho. subunits have been identified. It is generally accepted that native **GABA**.sub.A receptors are typically composed of 2.alpha., 2.beta., and 1.gamma. subunits (Pritchett & Seeburg Science 1989; 245:1389-1392 and Knight et. al.,. .

SUMM [0007] Benzodiazepines exert their pharmacological actions by interacting with the benzodiazepine binding sites associated with the **GABA**.sub.A receptor. In addition to the benzodiazepine site, the **GABA**.sub.A receptor contains sites of interaction for several other classes of drugs. These include a steroid binding site, a picrotoxin site, and the barbiturate site. The benzodiazepine site of the **GABA**.sub.A receptor is a distinct site on the receptor complex that does not overlap with the site of interaction for **GABA** or for other classes of drugs that bind to the receptor (see, e.g., Cooper, et al., The Biochemical Basis of. . . 145-148, Oxford University Press, New York). Early electrophysiological studies indicated that a major action of the benzodiazepines was enhancement of **GABAergic** inhibition. Compounds that selectively bind to the benzodiazepine site and enhance the ability of **GABA** to open **GABA**.sub.A receptor channels are agonists of **GABA** receptors. Other compounds that interact with the same site but negatively modulate the action of **GABA** are called inverse agonists. Compounds belonging to a third class bind selectively to the benzodiazepine site and yet have little or no effect on **GABA** activity, but can block the action of **GABA**.sub.A receptor agonists or inverse agonists that act at this site. These compounds are referred to as antagonists.

SUMM . . . long history of pharmaceutical use as anxiolytics, these compounds often exhibit a number of unwanted side effects. These may include **cognitive** impairment, sedation, ataxia, potentiation of ethanol effects, and a tendency for tolerance and drug dependence.

SUMM [0009] **GABA**.sub.A selective ligands may also act to potentiate the effects of certain other CNS active compounds. For example, there is evidence that selective serotonin reuptake inhibitors (SSRIs) may show greater antidepressant activity when used in combination with **GABA**.sub.A selective ligands than when used alone.

SUMM . . . Disclosed are certain novel compounds, particularly imidazoloisoquinolines that bind to cell surface receptors. Preferred compounds of the invention bind to **GABA** receptors, in particular these compounds possess affinity for the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A receptors. Also preferred are compounds that exhibit high selectivity to the benzodiazepine site of the **GABA**.sub.A receptor. These compounds are therefore considered to be of potential use in the

treatment of a broad array of diseases or disorders in patients, which are characterized by modulation of **GABA**.sub.A receptors.

SUMM [0011] Such diseases or disorders include, but are not limited to depression, anxiety, sleep disorders, **cognitive** disorders, low alertness, psychosis, obesity, pain, Parkinson's disease, **Alzheimer**'s disease, neurodegenerative diseases, movement disorders, Down's syndrome, and benzodiazepine overdoses.

SUMM [0015] Additionally this invention relates to the use of the compounds of the invention as probes for the localization of **GABA**.sub.A receptors in tissue sections.

SUMM [0087] This invention relates to heterocyclic derivatives that bind with high affinity and high selectivity to the benzodiazepine site of **GABA**.sub.A receptors, including human **GABA**.sub.A receptors.

SUMM [0094] Cognition impairment: cognition impairment, **Alzheimer**'s disease, Parkinson's disease, mild **cognitive** impairment (MCI) age-related **cognitive** decline (ARCD), stroke, traumatic brain injury, AIDS associate dementia, dementia associated with depression, anxiety or psychosis.

SUMM . . . that act as inverse agonists at the .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtype or .alpha..sub.1.beta..sub.2.gamma..sub.2 and .alpha..sub.5.beta..sub.3.gamma..sub.2 receptor subtypes are useful in treating **cognitive** disorders including those resulting from Down Syndrome, neurodegenerative diseases such as **Alzheimer**'s disease and Parkinson's disease, and stroke related dementia. Compounds of the invention that act as agonists at the .alpha..sub.1.beta..sub.2.gamma..sub.2 receptor. . .

SUMM . . . antagonists or corticotropin releasing factor receptor (CRF.sub.1) antagonists; for sleep disorders, melatonin receptor agonists; and for neurodegenerative disorders, such as **Alzheimer**'s dementia, nicotinic agonists, muscarinic agents, acetylcholinesterase inhibitors and dopamine receptor agonists. Particularly the invention provides a method of potentiating the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs) by administering a therapeutically effective amount of a **GABA** agonist compound of the invention in combination with an SSRI.

SUMM . . . or Le, et al., Alcohol and Alcoholism (1996) 31 Suppl. 127-132. Also see, the discussion of the use of the **GABA**.sub.A receptor ligand 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl) methyloxy-1,2,4-triazolo [3,4-a]phthalzine in combination with nicotinic agonists, muscarinic agonists, and acetylcholinesterase inhibitors, in PCT International publications Nos.. . . see in this regard PCT International publication No. WO 99/37303 for its discussion of the use of a class of **GABA**.sub.A receptor ligands, 1,2,4-triazolo[4,3-b]pyridazines, in combination with SSRIs.

SUMM [0098] The invention also pertains to methods of inhibiting the binding of benzodiazepine compounds, such as R015-1788, to the **GABA**.sub.A receptors which methods involve contacting a compound of the invention with cells expressing **GABA**.sub.A receptors, wherein the compound is present at a concentration sufficient to inhibit benzodiazepine binding to **GABA**.sub.A receptors in vitro. This method includes inhibiting the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of benzodiazepine compounds to **GABA**.sub.A receptors in vitro. In one embodiment, such methods are useful in treating benzodiazepine drug overdose. The amount of a compound that would be sufficient to inhibit the binding of a benzodiazepine compound to the **GABA**.sub.A receptor may be readily determined via a **GABA**.sub.A receptor binding assay, such as the assay described in Example 5. The **GABA**.sub.A receptors used to determine in vitro binding may be obtained from a variety of sources, for example from preparations of rat cortex or from cells expressing cloned human **GABA**.sub.A

receptors.

SUMM [0099] The invention also pertains to methods for altering the signal-transducing activity, particularly the chloride ion conductance, of **GABA**.sub.A receptors, said method comprising exposing cells expressing such receptors to a therapeutically effective amount of a compound of the invention. This method includes altering the signal-transducing activity of **GABA**.sub.A receptor s in vivo, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of **GABA** .sub.A receptors in vitro. The amount of a compound that would be sufficient to alter the signal-transducing activity of **GABA** .sub.A receptors may be determined via a **GABA**.sub.A receptor signal transduction assay, such as the assay described in Example 6.

SUMM [0100] The **GABA**.sub.A receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the **GABA**.sub.A receptor.

SUMM [0101] Labeled derivatives the **GABA**.sub.A receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single. . .

SUMM [0102] More particularly compounds of the invention may be used for demonstrating the presence of **GABA**.sub.A receptors in cell or tissue samples. This may be done by preparing a plurality of matched cell or tissue samples,. . . prepared as a control sample. The experimental sample is prepared by contacting (under conditions that permit binding of R015-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples that has not previously. . .

SUMM . . . in the at least one washed experimental sample than is detected in any of control samples demonstrates the presence of **GABA** .sub.A receptors in that experimental sample.

SUMM . . . most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of anxiety, depression, or **cognitive** impairment a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of sleep disorders a. . .

SUMM [0126] The present invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to **GABA**.sub.A receptor modulation, e.g., treatment of anxiety, depression, sleep disorders or **cognitive** impairment by **GABA**.sub.A receptor modulation.. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one **GABA**.sub.A receptor modulator as described supra and instructions (e.g., labeling) indicating the contained **GABA** .sub.A receptor ligand is to be used for treating a disorder responsive to **GABA**.sub.A receptor modulation in the patient.

DETD [0170] The high affinity and high selectivity of compounds of this invention for the benzodiazepine site of the **GABA**.sub.A receptor is confirmed using the binding assay described in Thomas and Tallman (J. Bio. Chem. 1981; 156:9838-9842, and J. Neurosci.. . .

DETD . . . compound of the invention act as an agonist, an antagonist, or an inverse agonist at the benzodiazepine site of the **GABA** .sub.A receptor.

DETD . . . subunit combination, sufficient message for each constituent subunit is injected to provide current amplitudes of >10 nA when 1 .mu.M **GABA** is applied.

DETD [0177] Compounds are evaluated against a **GABA** concentration that evokes <10% of the maximal evokable **GABA** current (e.g. 1 .mu.M-9 .mu.M). Each oocyte is exposed to increasing concentrations of compound in order to evaluate a concentration/effect relationship. Compound efficacy is calculated as a percent-change in current amplitude: 100*((Ic/I)-1), where Ic is the **GABA** evoked current amplitude observed in the presence of test compound and I is the **GABA** evoked current amplitude observed in the absence of the test compound.

DETD . . . completion of a concentration/effect curve. After washing the oocyte sufficiently to remove previously applied compound, the oocyte is exposed to **GABA**+1 .mu.M R015-1788, followed by exposure to **GABA**+1 .mu.M R015-1788+test compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in. . .

CLM What is claimed is:

28. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound or salt according to claim. . . the cell, wherein a detectable alteration of the electrophysiology of the cell indicates an alteration of the signal-transducing activity of **GABA**.sub.A receptors.

29. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound or salt according to claim 1 at a concentration sufficient to detectably alter the chloride conductance in vitro of cell expressing **GABA** .sub.a receptors.

31. The method of claim 30 wherein the cell is recombinantly expressing a heterologous **GABA**.sub.A receptor and the alteration of the electrophysiology of the cell is detected by intracellular recording or patch clamp recording.

34. A method for altering the signal-transducing activity of **GABA**.sub.A receptors, the method comprising exposing cells expressing **GABA**.sub.A receptors to a compound or salt according to claim 1 at a concentration sufficient to inhibit R015-1788 binding in vitro to cells expressing a human **GABA**.sub.A receptor.

35. A method for the treatment of anxiety, depression, a sleep disorder, or **Alzheimer**'s dementia comprising administering an effective amount of a compound or salt of claim 1 to a patient in need thereof.

. . .

36. A method for demonstrating the presence of **GABA**.sub.A receptors in cell or tissue samples, said method comprising: preparing a plurality of matched cell or tissue samples, preparing at least one control sample by contacting (under conditions that permit binding of R015-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . said first measured concentration, preparing at least one experimental sample by contacting (under conditions that permit binding of R015-1788 to **GABA**.sub.A receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously. . . washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of **GABA**.sub.A receptors in that experimental sample.

. . . and further comprising indicia comprising at least one of: instructions for using the composition to treat a patient suffering from **Alzheimer**'s dementia or instructions for using the composition to enhance cognition in a patient.

IT **78755-81-4**, R015-1788
(inhibition of binding; prepn. of imidazoloisoquinolines as GABAA receptor ligands)

=>

L7 ANSWER 8 OF 13 USPATFULL
AN 2002:221820 USPATFULL
TI Imidazole derivatives
IN Sanner, Mark A., Old Saybrook, CT, UNITED STATES
Helal, Chris J., Mystic, NJ, UNITED STATES
Cooper, Christoper B., Lawrenceville, NJ, UNITED STATES
Menniti, Frank S., Mystic, CT, UNITED STATES
Ahlijanian, Michael K., Mystic, CT, UNITED STATES
Villalobos, Anabella, Niantic, CT, UNITED STATES
Lau, Lit-Fui, Mystic, CT, UNITED STATES
Seymour, Patricia A., Westerly, RI, UNITED STATES
PI US 2002119963 A1 20020829
AI US 2001-919630 A1 20010731 (9)
PRAI US 2000-221724P 20000731 (60)
US 2000-228394P 20000828 (60)
US 2000-229437P 20000831 (60)
DT Utility
FS APPLICATION
LREP PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3078
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .
SUMM . . . The present invention further provides a pharmaceutical composition for treating in a mammal a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline comprising a cdk5 inhibitor and a COX-II inhibitor together in an amount effective in treating said disorder, and a. . .
SUMM [0113] This invention also provides a method for treating in a mammal a disorder selected from Alzheimer's disease, mild **cognitive** impariment, and age-related **cognitive** decline which method comprises administering to said mammal a cdk5 inhibitor and a COX-II inhibitor, wherein the combined amounts of. . .
SUMM [0123] This invention also provides a pharmaceutical composition for treating a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline in a mammal comprising a cdk5 inhibitor and an acetylcholinesterase inhibitor together in an amount effective in treating said. . .
SUMM [0124] This invention further provides a method for treating in a mammal a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline, which method comprises administering to said mammal a cdk5 inhibitor and an acetylcholinesterase inhibitor, wherein the combined amounts of. . .
SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .
SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease,

senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

SUMM . . . as compounds of formula 1, can also be administered in combination with a COX-II inhibitor for treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline. Specific examples of COX-II inhibitors useful in this aspect of the invention are provided above, wherein use of a. . . less than would be required on an individual basis to achieve the same desired effect in treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline.

SUMM [0200] This invention also provides a pharmaceutical composition and method for treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline comprising a cdk5 inhibitor, for example a compound of formula 1, and an acetylcholinesterase inhibitor. Acetylcholinesterase inhibitors are known. . . used in the above-described pharmaceutical composition or method. Examples of acetylcholinesterase inhibitors that can be used in this invention are **ARICEPT** (**donepezil**; U.S. Pat. No. 4,895,841); EXELON (**rivastigmine** ((S)-[N-ethyl-3-[1-(dimethylamino)ethyl]phenyl carbamate); U.S. Pat. No. 5,603,176 and U.S. Pat. No. 4,948,807); **metrifonate** ((2,2,2-trichloro-1-hydroxyethyl)phosphonic acid dimethyl ester; U.S. Pat. No. 2,701,225 and U.S. Pat. No. 4,950,658); galantamine (U.S. Pat. No. 4,663,318); physostigmine (Forest,. . .

SUMM . . . less than would be required on an individual basis to achieve the same desired effect in treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline.

SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

CLM What is claimed is:

. . . with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

42. A pharmaceutical composition for treating a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline in a mammal comprising a cdk5 inhibitor and an acetylcholinesterase inhibitor together in an amount effective in treating said. . .

44. A method for treating in a mammal a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline, which method comprises administering to said mammal a cdk5 inhibitor and an acetylcholinesterase inhibitor, wherein the combined amounts of. . .

. . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

. . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece,

brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

L7 ANSWER 9 OF 13 USPATFULL
AN 2002:192114 USPATFULL
TI Pyrazole derivatives
IN Sanner, Mark A., Old Saybrook, CT, UNITED STATES
Helal, Chris J., Mystic, CT, UNITED STATES
Cooper, Christopher B., Lawrenceville, NJ, UNITED STATES
Wager, Travis T., New London, CT, UNITED STATES
PI US 2002103185 A1 20020801
AI US 2001-941001 A1 20010828 (9)
PRAI US 2000-229415P 20000831 (60)
US 2000-232032P 20000912 (60)
DT Utility
FS APPLICATION
LREP PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4457
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .
SUMM . . . further provides a pharmaceutical composition for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline comprising a compound of formula 1 and a COX-II inhibitor together in an amount effective in treating said disorder,. . .
SUMM . . . invention also provides a method for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild **cognitive** imparіment, and age-related **cognitive** decline which method comprises administering to said mammal a compound of formula 1 and a COX-II inhibitor, wherein the combined. . .
SUMM [0349] This invention also provides a pharmaceutical composition for treating a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline in a mammal, including a human, comprising a compound of formula 1 and an acetylcholinesterase inhibitor together in an. . .
SUMM . . . invention further provides a method for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline, which method comprises administering to said mammal a compound of formula 1 and an acetylcholinesterase inhibitor, wherein the combined. . .
SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .
SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease,

senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

SUMM [0428] Compounds of formula 1 can also be administered in combination with a COX-II inhibitor for treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline. Specific examples of COX-II inhibitors useful in this aspect of the invention are provided above, wherein use of a. . . less than would be required on an individual basis to achieve the same desired effect in treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline.

SUMM [0437] This invention also provides a pharmaceutical composition and method for treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline comprising a compound of formula 1 and an acetylcholinesterase inhibitor. Acetylcholinesterase inhibitors are known in the art, and any. . . used in the above-described pharmaceutical composition or method. Examples of acetylcholinesterase inhibitors that can be used in this invention are **ARICEPT** (**donepezil**; U.S. Pat. No. 4,895,841); EXELON (**rivastigmine** ((S)-[N-ethyl-3-[1-(dimethylamino)ethyl]phenyl carbamate); U.S. Pat. Nos. 5,603,176 and 4,948,807); **metrifonate** ((2,2,2-trichloro-1-hydroxyethyl)phosphonic acid dimethyl ester; U.S. Pat. Nos. 2,701,225 and 4,950,658); galantamine (U.S. Pat. No. 4,663,318); physostigmine (Forest, USA); tacrine (1,2,3,4-tetrahydro-9-acridinamine;. . .

SUMM . . . less than would be required on an individual basis to achieve the same desired effect in treating Alzheimer's disease, mild **cognitive** impairment, or age-related **cognitive** decline.

SUMM . . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

CLM What is claimed is:

. . . with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

35. A pharmaceutical composition for treating a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline in a mammal comprising a compound according to claim 1 and an acetylcholinesterase inhibitor together in an amount effective. . .

36. A method for treating in a mammal a disorder selected from Alzheimer's disease, mild **cognitive** impairment, and age-related **cognitive** decline, which method comprises administering to said mammal a compound according to claim 1 and an acetylcholinesterase inhibitor, wherein the. . .

. . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

. . . AIDS induced dementia, migraine, hypoglycemia, urinary incontinece,

brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild **cognitive** impairment, age-related **cognitive** decline, emesis, corticobasal degeneration, dementia pugilistica, Down's syndrome, myotonic dystrophy, Niemann-Pick disease, Pick's disease, prion disease with tangles, progessive supranuclear. . .

L7 ANSWER 10 OF 13 USPATFULL
AN 2002:168258 USPATFULL
TI .alpha.-sulfonylamino hydroxamic acid inhibitors of matrix metalloproteinases for the treatment of peripheral or central nervous system disorders
IN Sahagan, Barbara G., Mystic, CT, United States
Villalobos, Anabella, Niantic, CT, United States
PA Pfizer Inc, New York, NY, United States (U.S. corporation)
PI US 6417229 B1 20020709
AI US 2000-671435 20000927 (9)
PRAI US 1999-157083P 19991001 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Criares, Theodore J.
LREP Richardson, Peter C., Ginsburg, Paul H., Myers, Jeffrey N.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1623
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related **cognitive** decline, mild **cognitive** impairment and prion diseases.
SUMM . . . head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related **cognitive** decline; mild **cognitive** impairment and prion diseases, and pharmaceutical compositions useful therefor.
SUMM . . . head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related **cognitive** decline; mild **cognitive** impairment and prion diseases, comprising the administration of small molecule inhibitors of MMP-9, MMP-2 or mixed MMP inhibitors which may. . .
SUMM . . . head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related **cognitive** decline; mild **cognitive** impairment and prion diseases in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound. . .
SUMM . . . head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral amyloid angiopathy, AIDS, age-related **cognitive** decline; mild **cognitive** impairment or a prion disease.
SUMM . . . nicotine agonist; a dopamine agonist; an inhibitor of neuronal nitric oxide synthase; an anti-Alzheimer's drug; an acetylcholinesterase inhibitor, such as **metrifonate**, **donepezil** (i.e., **Aricept**), Exelon (i.e., ENA 713 or **rivastigmine**), etc.; tetrahydroaminoacridine (i.e., Tacrine, Cognex, or THA); a COX-1 or COX-2 inhibitor, such as celecoxib (i.e., Celebrex), rofecoxib (i.e., Vioxx), . . .
CLM What is claimed is:
. . . disease, stroke/cerebral ischemia, head trauma, spinal cord injury, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's

disease, migraine, cerebral amyloid angiopathy, age-related **cognitive** decline; mild **cognitive** impairment and prion diseases, comprising the administration to said mammal a therapeutically effective amount of a compound of formula (I):. . .

L7 ANSWER 11 OF 13 USPATFULL
AN 2002:48594 USPATFULL
TI Methods and compositions for enhancing cellular function through protection of tissue components
IN Frey, William H., II, White Bear Lake, MN, UNITED STATES
Fawcett, John Randall, St. Paul, MN, UNITED STATES
PI US 2002028786 A1 20020307
AI US 2001-844450 A1 20010427 (9)
PRAI US 2000-200843P 20000501 (60)
US 2000-233263P 20000918 (60)
US 2000-233025P 20000915 (60)
DT Utility
FS APPLICATION
LREP GRAY, PLANT, MOOTY, MOOTY & BENNETT, P.A., P.O. BOX 2906, MINNEAPOLIS, MN, 55402-0906
CLMN Number of Claims: 80
ECL Exemplary Claim: 1
DRWN 20 Drawing Page(s)
LN.CNT 1624
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . of the invention can treat or prevent neurodegeneration, can improve memory and cognition, can treat or prevent brain deterioration or **cognitive** and memory loss associated with aging, or can treat or prevent Alzheimer's Disease, Parkinson's disease, Lewy body dementia, multiple sclerosis,. . .
DETD . . . mAChRs; with sodium and potassium ion channels; and effect the uptake, synthesis and release of neurotransmitters. Preferred anticholinesterase agents include **Aricept**, Exelon, **Metrifonate**, and the like.
DETD . . . human brain mAChR from inactivation and increase agonist binding indicates that these agents have therapeutic potential for the treatment of **cognitive** and memory disorders including those associated with aging, such as Alzheimer's disease.
CLM What is claimed is:
11. The method of claim 8, wherein the agent that directly or indirectly affects a mAChR comprises **donepezil**, **rivastigmine**, galanthamine, **metrifonate**, or a combination thereof.

55. The method of claim 52, wherein the agent that directly or indirectly affects a mAChR comprises **donepezil**, **rivastigmine**, galanthamine, **metrifonate**, or a combination thereof.

L7 ANSWER 12 OF 13 USPATFULL
AN 2002:27486 USPATFULL
TI Pharmaceutical composition for the treatment of attention deficit hyperactivity disorder (ADHD)
IN Coe, Jotham Wadsworth, Niantic, CT, UNITED STATES
Sands, Steven Bradley, Stonington, CT, UNITED STATES
Harrigan, Edmund Patrick, Old Lyme, CT, UNITED STATES
O'Neill, Brian Thomas, Old Saybrook, CT, UNITED STATES
Watsky, Eric Jacob, Stonington, CT, UNITED STATES
PI US 2002016334 A1 20020207
AI US 2001-865793 A1 20010525 (9)
PRAI US 2000-221718P 20000731 (60)
DT Utility
FS APPLICATION
LREP Paul H. Ginsburg, Pfizer Inc., 235 East 42nd Street, 20th Floor, New

York, NY, 10017-5755
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1580
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . E., Psychopharmacology 108:417-431, 1992). In animal studies, nicotine can reverse deficits in working memory in brain-lesioned rats (Levin et al., **Cognitive** Brain Research 1:137-143, 1993) and also improves performance on serial choice tasks which are thought to partially model symptoms of. . .
SUMM . . . Examples of cholinesterase inhibitors that can be used in the compositions of this invention include, but are not limited to **donepezil** (**Aricept**), tacrine (Cognx.TM.), **rivastigmine** (Exelon.TM.), physostigmine (Synapton), galanthamine (Reminyl), **metrifonate** (Promem), neostigmine (Prostigmin), and icopezil and their pharmaceutically acceptable salts.
DETD . . . the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as **cognitive** function, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular). The following. . .
DETD [0347] For **donepezil** (**Aricept**.TM.) the range is about 0.01 to about 0.15 mg/kg/day
DETD [0349] For **rivastigmine** (Exelon.TM.) the range is about 0.1 to about 0.1 mg/kg/day
DETD [0352] For **metrifonate** (Promem) the range is about 0.1 to about 5.0 mg/kg/day
CLM What is claimed is:
10. The pharmaceutical composition according to claim 1, wherein the cholinesterase inhibitors are selected from **donepezil**, tacrine, **rivastigmine**, physostigmine, galanthamine, **metrifonate**, neostigmine, and icopezil and their pharmaceutically acceptable salts.

20. The method according to claim 11 wherein the cholinesterase inhibitors are selected from **donepezil**, tacrine, **rivastigmine**, physostigmine, galanthamine, **metrifonate** , neostigmine, and copezil and their pharmaceutically acceptable salts.

L7 ANSWER 13 OF 13 USPATFULL
AN 2001:194434 USPATFULL
TI Pharmaceutical composition and method of treatment of diseases of **cognitive** dysfunction in a mammal
IN Coe, Jotham Wadsworth, Niantic, CT, United States
Sands, Steven Bradley, Stonington, CT, United States
Harrigan, Edmund Patrick, Old Lyme, CT, United States
O'Neill, Brian Thomas, Old Saybrook, CT, United States
Watsky, Eric Jacob, Stonington, CT, United States
PI US 2001036949 A1 20011101
AI US 2001-760966 A1 20010116 (9)
PRAI US 2000-202799P 20000509 (60)
DT Utility
FS APPLICATION
LREP Paul H. Ginsburg, Pfizer Inc, 235 East 42nd Street, 20th Floor, New York, NY, 10017-5755
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1728
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Pharmaceutical composition and method of treatment of diseases of **cognitive** dysfunction in a mammal

AB A pharmaceutical composition and method of treatment of diseases of **cognitive** dysfunction in a mammal comprising administration of a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; and an. . . muscarinic agonist are present in amounts that render the composition effective enhancing cognition or in the treatment of diseases of **cognitive** dysfunction including but not limited to Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and schizophrenia. The method of using these. . .

SUMM [0001] The present invention relates to pharmaceutical compositions for the prevention and/or treatment of diseases of **cognitive** dysfunction in a mammal comprising nicotine receptor partial agonists (NRPA) in combination with acetylcholinesterase inhibitors, butylcholinesterase inhibitors, estrogen, selective estrogen. . . agonists and a pharmaceutically acceptable carrier. The pharmaceutical compositions are useful in enhancing memory in patients suffering from diseases of **cognitive** dysfunction such as, but not limited to, Alzheimer's Disease (AD), mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's disease, stroke, traumatic brain injury (TBI), AIDS associated dementia and schizophrenia.

SUMM [0002] **Cognitive** and/or degenerative brain disorders are characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually. . .

SUMM [0003] Alzheimer's Disease is associated with degeneration of cholinergic neurons in the basal forebrain that play a fundamental role in **cognitive** functions, including memory [Becker et al., Drug Development Research, 12, 163-195 (1988)]. As a result of such degeneration, patients suffering. . .

SUMM [0005] NRPAs are expected to improve **cognitive** function in the above mentioned conditions. Referenced herein are well-documented findings that cholinergic mechanisms are important for normal **cognitive** functioning and that cholinergic hypofunction accompanies the **cognitive** deficits associated with Alzheimer's Disease (AD). It has been shown previously that nicotine administration improves some aspects of **cognitive** performance in both animal models of **cognitive** function and in patients with AD [Wilson et al., Pharmacology Biochemistry and Behavior, 51, 509-514 (1995); Arneric et al., Alzheimer. . .

SUMM . . . with predicted peak levels of acetylcholine in the brain. They discuss the efficacy of three known acetylcholinesterase inhibitors physostigmine (Synapton), **metrifonate**, and tetrahydroaminoacridine. The development of specific acetylcholinesterase inhibitors has greatly improved the treatment options available for patients suffering from degenerative neurological disorders (e.g. **Aricept**).

SUMM . . . which result in cognition enhancement. Estrogen has been shown to have protective effects in both in vivo model systems of **cognitive** dysfunction as well as human clinical studies. Singh, et al. [Brain Research, 644, 305-312 (1994)] demonstrates a decline of **cognitive** function in the ovarectomized rat which can be prevented by administration of estrogen. Fifteen clinical studies examining the role of estrogen replacement therapy in cognition demonstrate statistically significant improvements in **cognitive** function [Haskell et al., Journal of Clinical Epidemiology, 50(11), 1249-1264 (1997)]. Such combinations are useful in the treatment of disorders associated with cognition impairment including, but not limited to, Alzheimer's Disease (AD), mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's disease, stroke, traumatic brain injury (TBI) AIDS associated dementia and schizophrenia.

SUMM . . . use of NRPAs and muscarinic agonists which result in cognition enhancement. Muscarinic and nicotinic agonists have been reported to

enhance **cognitive** tasks in animal models and in humans. Schwarz et al., Journal of Pharmacology & Experimental Therapeutics 291: 812-22 (1999); Veroff. . .

SUMM . . . be useful in the treatment of disorders associated with cognition impairment including, but not limited to, Alzheimer's Disease (AD), mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's disease, stroke, traumatic brain injury (TBI) AIDS associated dementia and schizophrenia.

SUMM [0010] The present invention relates to a pharmaceutical composition for the enhancement of cognition or the treatment of disorders involving **cognitive** dysfunction in a mammal comprising (a) a nicotine receptor partial agonist (NRPA) or a pharmaceutical acceptable salt thereof; (b) an. . . are present in amounts that render the composition effective in the enhancement of cognition or the treatment of disorders of **cognitive** dysfunction.

SUMM [0142] The acetylcholinesterase or butylcholinesterase inhibitor are selected from donepizil (**Aricept**.TM.), tacrine (Cognex.TM.), **rivastigmine** (Exelon.TM.), physostigmine (Synapton), galanthamine (Reminyl), **metrifonate** (Promem), quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, huperzine A and icopezil. U.S. patent application Ser. No. 07/639,614. . .

SUMM [0146] The pharmaceutical compositions are useful in the enhancement of cognition or the treatment of disorders involving **cognitive** dysfunction including but not limited to Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease, dementia, Huntington's disease, stroke, traumatic brain injury (TBI), AIDS associated dementia and schizophrenia.

SUMM [0147] Another aspect of this invention is a method of enhancing cognition or the treatment of a disorder involving **cognitive** dysfunction in a mammal comprising administering to the mammal, an amount of (a) a nicotine receptor partial agonist or a. . . render the combination of the two ingredients effective in cognition or the enhancement of a disorder involving treatment of disorders **cognitive** dysfunction.

SUMM . . . aspect of this method is wherein the NRPA is in combination with an acetylcholinesterase or butylcholinesterase inhibitor selected from donepizil (**Aricept**.TM.), tacrine (Cognex.TM.) **rivastigmine** (Exelon.TM.), physostigmine (Synapton), galanthamine (Reminyl), **metrifonate** (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, huperzine A and icopezil or a pharmaceutically acceptable salt of. . .

SUMM [0284] The pharmaceutical composition is used for enhancing cognition or treating a disorder involving **cognitive** dysfunction, including but not limited to, Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's disease, Stroke, TBI, AIDS associated dementia and Schzophrenia in a mammal, including a human. The method comprises administering to said mammal a **cognitive** dysfunction attenuating effective amount of the above pharmaceutical composition comprising (a) a nicotine receptor partial agonist or a pharmaceutically acceptable. . .

SUMM [0285] A method of treating a disorder or condition selected from the group consisting of Alzheimer Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and Schizophrenia comprises administering to a mammal. . . (b) above are administered in amounts that render the combination of the two ingredients effective in treating Alzheimer's Disease, mild **Cognitive** impairment, age-related **cognitive** decline, Vascular dementia, Huntington's Disease,

Strole, TBI, AIDS associated dementia and Schizophrenia.

DETD [0290] An acetylcholinesterase or a butylcholinesterase inhibitor or a pharmaceutically acceptable salt of the foregoing compounds such as donepizil (**Aricept**.TM.), tacrine (Cognex.TM.) **rivastigmine** (Exelon.TM.), physostigmine (Synapton),galanthamine (Reminyl), **metrifonate** (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, huperzine A and icopezil may be used in this invention.

DETD . . . utility of the compounds of the present invention as medical agents in the treatment of conditions which present with low **cognitive** function (such as Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's disease, stroke, traumatic brain injury (TBI), AIDS associated dementia and schizophrenia) in mammals. . . below: nicotine receptor binding assay, dopamine turnover, acetylcholinesterase inhibitor protocol, in vitro estrogen receptor binding assay and muscarinic receptor binding. **Cognitive** function of the agents themselves or of the combination agents in mammals is measured in the radial arm maze in. .

DETD ASSAYS FOR **COGNITIVE** DYSFUNCTION

DETD . . . session. It is possible to separate two main components of the DMTS task, a test of memory recall and a **cognitive** component which tests the abstract conceptualization of "matching". Baseline runs are generally performed on Mondays, with drug administered on Tuesdays. . .

DETD . . . compounds employed in the present invention as medicinal agents include neuronal nicotinic receptor binding, dopamine turnover, and animal models of **cognitive** impairment. Such assays also provide a means whereby the activities of the compounds of this invention can be compared between. . .

DETD . . . the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as **cognitive** function, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular). The following. . .

DETD [0334] For **donepezil** (**Aricept**.TM.) the range is 0.01 to 0.15 mg/kg/day

DETD [0336] For **rivastigmine** (Exelon.TM.) the range is 0.1 to 0.1 mg/kg/day

DETD [0339] For **metrifonate** (Promem) the range is 0.1 to 5.0 mg/kg/day

CLM What is claimed is:

1. A pharmaceutical composition for the enhancement of cognition or the treatment of disorders involving **cognitive** dysfunction in a mammal comprising: (a) a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; (b) an acetylcholinesterase. . . are present in amounts that render the composition effective in the enhancement of cognition or the treatment of disorders involving **cognitive** dysfunction.

. . . 4. A pharmaceutical composition according to claim 1 wherein the acetylcholinesterase inhibitor or the butylcholinesterase inhibitor is selected from donepizil (**Aricept**.TM.), tacrine (Cognex.TM.) **rivastigmine** (Exelon.TM.), physostigmine (Synapton), galanthamine (Reminyl), **metrifonate** (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, huperzine A and icopezil or a pharmaceutically acceptable salt of. . .

8. A pharmaceutical composition according to claim 1 wherein diseases of **cognitive** dysfunction are selected from, but are not limited to, Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease

dementia, Huntington's disease, stroke, traumatic brain injury (TBI), AIDS associated dementia and schizophrenia.

9. A method of enhancing cognition or treating a disorder involving **cognitive** dysfunction in a mammal comprising administering to said mammal, an amount of a. a nicotine receptor partial agonist or a. . . (b) are administered in amounts that render the combination of the two ingredients effective in the treatment of diseases of **cognitive** dysfunction.

12. A method according to claim 9 wherein the acetylcholinesterase inhibitor or butylcholinesterase inhibitor is selected from donepizil (**Aricept**.TM.), tacrine (Cognex.TM.) **rivastigmine** (Exelon.TM.), physostigmine (Synapton), galanthamine (Reminyl), **metrifonate** (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, huperzine A and icopezil or a pharmaceutically acceptable salt of. . .

16. A method according to claim 9 wherein the disorders of **cognitive** dysfunction are selected from, but not limited to, Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline vascular dementia, Parkinson's disease dementia, Huntington's disease, stroke traumatic brain injury (TBI), AIDS associated dementia and schizophrenia.

21. A pharmaceutical composition for enhancing cognition or treating a disorder involving **cognitive** dysfunction, including but not limited to, Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and schizophrenia in a mammal, including a human, the method comprises administering to said mammal a **cognitive** dysfunction attenuating effective amount of a pharmaceutical composition comprising: (a) a nicotine receptor partial agonist or a pharmaceutically acceptable salt. . .

22. A method of treating a disorder or conditon selected from the group consisting of Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and schizophrenia comprising adminstering to said mammal;. . . (b) above are administered in amounts that render the combination of the two ingredients effective in treating Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and schizophrenia.

=>

L19 ANSWER 1 OF 5 USPATFULL
AN 2002:192134 USPATFULL
TI Muscarinic antagonists
IN Lowe, Derek, Scotch Plains, NJ, UNITED STATES
Chang, Wei, Livingston, NJ, UNITED STATES
Kozlowski, Joseph, Princeton, NJ, UNITED STATES
Berger, Joel G., Cedar Grove, NJ, UNITED STATES
McQuade, Robert, Scotch Plains, NJ, UNITED STATES
Barnett, Allen, Pine Brook, NJ, UNITED STATES
Sherlock, Margaret, Bloomfield, NJ, UNITED STATES
Tom, Wing, Cedar Grove, NJ, UNITED STATES
Dugar, Sundeep, Bridgewater, NJ, UNITED STATES
Chen, Lian-Yong, Edison, NJ, UNITED STATES
Clader, John W., Cranford, NJ, UNITED STATES
Chackalamannil, Samuel, East Brunswick, NJ, UNITED STATES
Yuguang, Wang, North Brunswick, NJ, UNITED STATES
McCombie, Stuart W., Caldwell, NJ, UNITED STATES
Tagat, Jayaram R., Westfield, NJ, UNITED STATES
Vice, Susan F., Mountainside, NJ, UNITED STATES
Vaccaro, Wayne, Yardley, PA, UNITED STATES
Green, Michael J., Skillman, NJ, UNITED STATES
Browne, Margaret E., Bloomfield, NJ, UNITED STATES
Asberom, Theodros, West Orange, NJ, UNITED STATES
PI US 2002103205 A1 20020801
US 6498168 B2 20021224
AI US 2001-902849 A1 20010711 (9)
RLI Division of Ser. No. US 2000-482168, filed on 12 Jan 2000, GRANTED, Pat. No. US 6288068 Division of Ser. No. US 1998-195742, filed on 19 Nov 1998, GRANTED, Pat. No. US 6037352 Division of Ser. No. US 1996-602403, filed on 16 Feb 1996, GRANTED, Pat. No. US 5883096 Continuation-in-part of Ser. No. US 1995-457712, filed on 2 Jun 1995, ABANDONED Continuation-in-part of Ser. No. US 1995-392697, filed on 23 Feb 1995, ABANDONED
DT Utility
FS APPLICATION
LREP SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530
CLMN Number of Claims: 26
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 3263
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . R.sup.2, R.sup.3, R.sup.4, R.sup.21, R.sup.27, R.sup.28, X, Y, and Z are as defined herein are muscarinic antagonists useful for treating **cognitive** disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula or other compounds capable of enhancing acetylcholine release with **acetylcholinesterase** inhibitors.
DRWD [0053] FIG. 3 illustrates the effect of 3 mg/kg of **Tacrine** (i.p. administration) on ACh release from striatum of conscious rat.
DRWD . . . plot similar to FIG. 4 for 1 mg/kg of a compound of this invention in combination with 3 mg/kg of **Tacrine** (both i.p. administration).
DETD . . . formula I in combination with an acetylcholinesterase (ACh'ase) inhibitor have a synergistic effect on ACh release, as shown below. Here **Tacrine** was used as the ACh'ase inhibitor.

From Striatum of Conscious Rat

Dose	Peak ACh release as % increase over Baseline (FIGS. 3 to 5)

Tacrine 3 mg/kg (i.p.) 30 (FIG. 3)
Compound 169 1 mg/kg (i.p.) 40 (FIG. 4)
Tacrine 3 mg/kg and 130 (FIG. 5)
Compound 169 1 mg/kg (i.p.)

DETD [0147] As shown immediately above, when administered in combination, compound 169 and **tacrine** produce a synergistic increase in ACh release.

L19 ANSWER 2 OF 5 USPATFULL
AN 2001:194434 USPATFULL
TI Pharmaceutical composition and method of treatment of diseases of cognitive dysfunction in a mammal
IN Coe, Jotham Wadsworth, Niantic, CT, United States
Sands, Steven Bradley, Stonington, CT, United States
Harrigan, Edmund Patrick, Old Lyme, CT, United States
O'Neill, Brian Thomas, Old Saybrook, CT, United States
Watsky, Eric Jacob, Stonington, CT, United States
PI US 2001036949 A1 20011101
AI US 2001-760966 A1 20010116 (9)
PRAI US 2000-202799P 20000509 (60)
DT Utility
FS APPLICATION
LREP Paul H. Ginsburg, Pfizer Inc, 235 East 42nd Street, 20th Floor, New York, NY, 10017-5755
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1728
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical composition and method of treatment of diseases of **cognitive** dysfunction in a mammal comprising administration of a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; and an **acetylcholinesterase** inhibitor, butylcholinesterase inhibitor, an estrogenic agent, selective estrogen receptor modulator or muscarinic agonist or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The nicotine receptor partial agonist and **acetylcholinesterase** inhibitor, butylcholinesterase inhibitor, estrogen, selective estrogen receptor modulator or muscarinic agonist are present in amounts that render the composition effective enhancing cognition or in the treatment of diseases of **cognitive** dysfunction including but not limited to Alzheimer's Disease, mild **cognitive** impairment, age-related **cognitive** decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS associated dementia and schizophrenia. The method of using these. . .
SUMM . . . to coincide with predicted peak levels of acetylcholine in the brain. They discuss the efficacy of three known acetylcholinesterase inhibitors **physostigmine** (Synapton), metrifonate, and tetrahydroaminoacridine. The development of specific acetylcholinesterase inhibitors has greatly improved the treatment options available for patients suffering. . .
SUMM [0142] The acetylcholinesterase or butylcholinesterase inhibitor are selected from donepizil (Aricept.TM.), **tacrine** (Cognex.TM.), rivastigmine (Exelon.TM.), **physostigmine** (Synapton), galanthamine (Reminyl), metrifonate (Promem), quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, **huperzine** A and **icopezil**. U.S. patent application Ser. No. 07/639,614 filed Jan. 10, 1991; U.S. patent application Ser. No. 07/676,918 filed Mar. 28, 1991;. . .
SUMM . . . of this method is wherein the NRPA is in combination with an acetylcholinesterase or butylcholinesterase inhibitor selected from donepizil (Aricept.TM.), **tacrine** (Cognex.TM.) rivastigmine (Exelon.TM.), **physostigmine** (Synapton), galanthamine

(Reminyl), metrifonate (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, **huperzine** A and **icopezil** or a pharmaceutically acceptable salt of one of the foregoing compounds.

DETD [0290] An acetylcholinesterase or a butylcholinesterase inhibitor or a pharmaceutically acceptable salt of the foregoing compounds such as donepizil (Aricept.TM.), **tacrine** (Cognex.TM.) rivastigmine (Exelon.TM.), **physostigmine** (Synapton),galanthamine (Reminyl), metrifonate (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, **huperzine** A and **icopezil** may be used in this invention.

DETD . . . Ind.) and superfused at a rate 3 mL/minute. The dialysis fluid was a Ringer's buffer (pH 7.2) containing 500 nM **physostigmine** to reduce degradation of Ach by AChE. Fractions (60 .mu.l) were collected every 20 minutes for 2 hours before drug. . .

DETD [0335] For **tacrine** (Cognex.TM.) the range is 0.1 to 2.3 mg/kg/day

DETD [0337] For **physostigmine** (Synapton) the range is 0.01 to 0.4 mg/kg/day

DETD [0349] For **huperzine** A the range is 0.01 to 1.0 mg/kg/day

DETD [0350] For **icopezil** the range is 0.001 to 0.01 mg/kg/day

CLM What is claimed is:

. . . A pharmaceutical composition according to claim 1 wherein the acetylcholinesterase inhibitor or the butylcholinesterase inhibitor is selected from donepizil (Aricept.TM.), **tacrine** (Cognex.TM.) rivastigmine (Exelon.TM.), **physostigmine** (Synapton), galanthamine (Reminyl), metrifonate (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, **huperzine** A and **icopezil** or a pharmaceutically acceptable salt of one of the foregoing compounds.

12. A method according to claim 9 wherein the acetylcholinesterase inhibitor or butylcholinesterase inhibitor is selected from donepizil (Aricept.TM.), **tacrine** (Cognex.TM.) rivastigmine (Exelon.TM.), **physostigmine** (Synapton), galanthamine (Reminyl), metrifonate (Promem) quilostigmine, tolserine, thiatolserine, cymserine, thiacymserine, neostigmine, eseroline, zifrosilone, mestinon, **huperzine** A and **icopezil** or a pharmaceutically acceptable salt of one of the foregoing compounds.

L19 ANSWER 3 OF 5 USPATFULL

AN 2001:152965 USPATFULL

TI Muscarinic antagonists

IN Lowe, Derek, Scotch Plains, NJ, United States
Chang, Wei, Livingston, NJ, United States
Kozlowski, Joseph, Princeton, NJ, United States
Berger, Joel G., Cedar Grove, NJ, United States
McQuade, Robert, Scotch Plains, NJ, United States
Barnett, Allen, Pine Brook, NJ, United States
Sherlock, Margaret, Bloomfield, NJ, United States
Tom, Wing, Cedar Grove, NJ, United States
Dugar, Sundeep, Bridgewater, NJ, United States
Chen, Lian-Yong, Edison, NJ, United States
Clader, John W, Cranford, NJ, United States
Chackalamannil, Samuel, East Brunswick, NJ, United States
Yuguang, Wang, North Brunswick, NJ, United States
McCombie, Stuart W., Caldwell, NJ, United States
Tagat, Javaram R., Westfield, NJ, United States
Vice, Susan F., Mountainside, NJ, United States
Vaccaro, Wayne, Yardley, PA, United States
Green, Michael J., Skillman, NJ, United States
Browne, Margaret E., Bloomfield, NJ, United States

Asberom, Theodros, West Orange, NJ, United States
PA Schering Corporation, Kenilworth, NJ, United States (U.S. corporation)
PI US 6288068 B1 20010911
AI US 2000-482168 20000112 (9)
RLI Division of Ser. No. US 1998-195742, filed on 19 Nov 1998, now patented, Pat. No. US 6037352 Division of Ser. No. US 1996-602403, filed on 16 Feb 1996, now patented, Pat. No. US 5883096 Continuation-in-part of Ser. No. US 1995-457712, filed on 2 Jun 1995, now abandoned Continuation-in-part of Ser. No. US 1995-392697, filed on 23 Feb 1995, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Qazi, Sabiha
LREP Magatti, Anita W.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 2861
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . R.sup.2, R.sup.3, R.sup.4, R.sup.21, R.sup.27, R.sup.28, X, Y, and Z are as defined herein are muscarinic antagonists useful for treating **cognitive** disorders such as Alheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula or other compounds capable of enhancing acetylcholine release with **acetylcholinesterase** inhibitors.
DRWD FIG. 3 illustrates the effect of 3 mg/kg of **Tacrine** (i.p. administration) on ACh release from striatum of conscious rat.
DRWD . . . plot similar to FIG. 4 for 1 mg/kg of a compound of this invention in combination with 3 mg/kg of **Tacrine** (both i.p. administration).
DETD . . . formula I in combination with an acetylcholinesterase (ACh'ase) inhibitor have a synergistic effect on ACh release, as shown below. Here **Tacrine** was used as the ACh'ase inhibitor.
DETD From Striatum of Conscious Rat

Dose		Peak ACh release as % increase over Baseline (FIGS. 3 to 5)
Tacrine	3 mg/kg (i.p.)	30 (FIG. 3)
Compound 169	1 mg/kg (i.p.)	40 (FIG. 4)
Tacrine	3 mg/kg and	130 (FIG. 5)
Compound 169	1 mg/kg (i.p.)	

DETD As shown immediately above, when administered in combination, compound 169 and **tacrine** produce a synergistic increase in ACh release.

L19 ANSWER 4 OF 5 USPATFULL
AN 2000:31426 USPATFULL
TI Muscarinic antagonists
IN Lowe, Derek, Scotch Plains, NJ, United States
Chang, Wei, Livingston, NJ, United States
Kozlowski, Joseph, Princeton, NJ, United States
Berger, Joel G., Cedar Grove, NJ, United States
McQuade, Robert, Scotch Plains, NJ, United States
Barnett, Allen, Pine Brook, NJ, United States
Sherlock, Margaret, Bloomfield, NJ, United States
Tom, Wing, Cedar Grove, NJ, United States
Dugar, Sundeep, Bridgewater, NJ, United States
Chen, Lian-Yong, Edison, NJ, United States
Clader, John W, Cranford, NJ, United States
Chackalamannil, Samuel, East Brunswick, NJ, United States
Yuguang, Wang, North Brunswick, NJ, United States
McCombie, Stuart W., Caldwell, NJ, United States
Tagat, Jayaram R., Westfield, NJ, United States
Vice, Susan F., Mountainside, NJ, United States
Vaccaro, Wayne, Yardley, PA, United States

Green, Michael J., Skillman, NJ, United States
Browne, Margaret E., Bloomfield, NJ, United States
Asberom, Theodros, West Orange, NJ, United States
PA Schering Corporation, Kenilworth, NJ, United States (U.S. corporation)
PI US 6037352 20000314
AI US 1998-195742 19981119 (9)
RLI Division of Ser. No. US 1996-602403, filed on 16 Feb 1996, now patented, Pat. No. US 5883096 which is a continuation-in-part of Ser. No. US 1995-457712, filed on 2 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-392697, filed on 23 Feb 1995, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Qazi, Sabiha N.
LREP Magatti, Anita W.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 3330
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB . . . R.sup.2, R.sup.3, R.sup.4, R.sup.21, R.sup.27, R.sup.28, X, Y, and Z are as defined herein are muscarinic antagonists useful for treating **cognitive** disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula or other compounds capable of enhancing acetylcholine release with **acetylcholinesterase** inhibitors.
DRWD FIG. 3 illustrates the effect of 3 mg/kg of **Tacrine** (i.p. administration) on ACh release from striatum of conscious rat.
DRWD . . . plot similar to FIG. 4 for 1 mg/kg of a compound of this invention in combination with 3 mg/kg of **Tacrine** (both i.p. administration).
DETD . . . formula I in combination with an acetylcholinesterase (ACh'ase) inhibitor have a synergistic effect on ACh release, as shown below. Here **Tacrine** was used as the ACh'ase inhibitor.

DETD

Dose	Peak ACh release as % increase over Baseline (FIGS. 3 to 5)
Tacrine 3 mg/kg (i.p.)	30 (FIG. 3)
Compound 169 1 mg/kg (i.p.)	40 (FIG. 4)
Tacrine 3 mg/kg and Compound 169 1 mg/kg (i.p.)	130 (FIG. 5)

DETD As shown immediately above, when administered in combination, compound 169 and **tacrine** produce a synergistic increase in ACh release.

L19 ANSWER 5 OF 5 USPATFULL
AN 1999:33999 USPATFULL
TI Muscarinic antagonists
IN Lowe, Derek, Scotch Plains, NJ, United States
Chang, Wei, Livingston, NJ, United States
Kozlowski, Joseph, Princeton, NJ, United States
Berger, Joel G., Cedar Grove, NJ, United States
McQuade, Robert, Scotch Plains, NJ, United States
Barnett, Allen, Pine Brook, NJ, United States
Sherlock, Margaret, Bloomfield, NJ, United States
Tom, Wing, Cedar Grove, NJ, United States
Dugar, Sundeep, Bridgewater, NJ, United States
Chen, Lian-Yong, Edison, NJ, United States
Clader, John W., Cranford, NJ, United States

Chackalamannil, Samuel, East Brunswick, NJ, United States
Yuguang, Wang, North Brunswick, NJ, United States
McCombie, Stuart W., Caldwell, NJ, United States
Tagat, Jayaram R., Westfield, NJ, United States
Vice, Susan F., Mountainside, NJ, United States
Vaccaro, Wayne, Yardley, PA, United States
Green, Michael J., Skillman, NJ, United States
Browne, Margaret E., Bloomfield, NJ, United States
Asberom, Theodros, West Orange, NJ, United States

PA Schering Corporation, Kenilworth, NJ, United States (U.S. corporation)

PI US 5883096 19990316
AI US 1996-602403 19960216 (8)
RLI Continuation-in-part of Ser. No. US 1995-457712, filed on 2 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-392697, filed on 23 Feb 1995, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Dees, Jose'G.; Assistant Examiner: Qazi, Sabiha N.
LREP Magatti, Anita W.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 3263

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB R.sup.3, R.sup.4, R.sup.5, R.sup.20, R.sup.27 and R.sup.28 are as defined in the specification; are muscarinic antagonists useful for treating **cognitive** disorders such as Alzheimer's disease; pharmaceutical compositions and methods of preparation are also disclosed, as well as synergistic combinations of compounds of the above formula or other compounds capable of enhancing acetylcholine release with **acetylcholinesterase** inhibitors.

DRWD FIG. 3 illustrates the effect of 3 mg/kg of **Tacrine** (i.p. administration) on ACh release from striatum of conscious rat.

DRWD . . . plot similar to FIG. 4 for 1 mg/kg of a compound of this invention in combination with 3 mg/kg of **Tacrine** (both i.p. administration).

DETD . . . formula I in combination with an acetylcholinesterase (ACh'ase) inhibitor have a synergistic effect on ACh release, as shown below. Here **Tacrine** was used as the ACh'ase inhibitor.

DETD

From Striatum of Conscious Rat

Dose	Peak ACh release as % increase over Baseline (FIGS. 3 to 5)
Tacrine 3 mg/kg (i.p.)	30 (FIG. 3)
Compound 169 1 mg/kg (i.p.)	40 (FIG. 4)
Tacrine 3 mg/kg and Compound 169 1 mg/kg (i.p.)	130 (FIG. 5)

DETD As shown immediately above, when administered in combination, compound 169 and **tacrine** produce a synergistic increase in ACh release.

=>

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E
  22 FILES SEARCHED...
'2000' NOT A VALID FIELD CODE
'2000' NOT A VALID FIELD CODE
'2000' NOT A VALID FIELD CODE
  26 FILES SEARCHED...
'2000' NOT A VALID FIELD CODE
'2000' NOT A VALID FIELD CODE
  33 FILES SEARCHED...
  34 FILES SEARCHED...
L8          5 L7 AND PD<2000

=> d l8 1-5 ab

L8   ANSWER 1 OF 5  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB   Donepezil is a new cognitive enhancer whose mechanism
     of action consists in reversible specific inhibition of
     acetylcholinesterase activity. The doses of 5 and 10 mg of
     donepezil had the effect of blocking acetylchotinesterase in
     erythrocytes (correlating closely with its effect in the CNS) in 64 and 75
     % respectively. Other effects of donepezil include indirect
     stimulation of muscarine and nicotine receptors by increasing the
     concentration of acetylcholine in CNS synapses, increasing the
     extraneuronal concentration not only of acetylcholine, but also of
     noradrenaline and eventually dopamine, decreasing the permeability of
     oxygen radicals through neurone membranes, and improving the glucose
     metabolism in CNS. The absorption of donepezil from the
     gastrointestinal tract is complete and remains unaffected by food intake.
     The maximum plasmatic concentration of the preparation is reached within 3
     to 5 hours after administration; the drug binds with low affinity to
     plasma proteins. The elimination half-life of donepezil is 70 to
     80 hours, the steady state serum concentration being reached within 14 to
     21 days of treatment. Donepezil is characterised by linear
     pharmacokinetics. Its metabolite 6-O-desmethyl-donepezil is
     biologically active. The proof of therapeutic efficacy of
     donepezil is based on 4 placebo-controlled clinical studies which
     included the total of 1920 patients with the diagnosis of Alzheimer's
     disease of mild to medium severity, treated for 12 to 26 weeks. From the
     3rd to 12th week on, in approx. 21 to 38% of patients an improvement of
     cognitive and behavioural functions was observed. In 20 to 45% of
     patients stabilisation of state occurred, which also can be interpreted as
     therapeutic success in dealing with a disorder of such
     progression as Alzheimer's disease. Psychic state improvement was observed
     especially in milder dementia, while in patients suffering from the
     disease of medium severity only stabilisation of symptoms was observed.
     The discontinuation of donepezil administration was followed by
     a slow state deterioration, which shows that the drug does not treat the
     cause of Alzheimer's disease. In an open continuation of these studies
     donepezil was administered to 133 patients for intervals of up to
     2 years. There are other studies which have not yet been finished. The
     initial improvement of starting values of cognitive and
     behavioural functions lasted from 26 to 38 weeks, being followed by
     gradual deterioration of psychic state. Donepezil had the
     capacity to stabilise symptomatically and rewind the biological life of
     the patients back by 6 to 12 months and thus to slow down the course of
     Alzheimer's disease in comparison with untreated patients. The conducted
     studies have shown that the minimum efficient dose of donepezil
     is 5 mg (administered once a day thanks to its long elimination
     half-life). In some studies the dose of 10 mg per day was found to be more
     efficient than the lower dose. Donepezil was very well tolerated
     by patients. Adverse effects observed in 5 to 20% of patients most often
     included nausea, diarrhoea, vomiting, muscle cramps, fatigue, and
     insomnia. The producer recommends careful administration especially to
     patients suffering from peptic ulcers, bronchial asthma and cordial
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conduction disorders. In cases of intoxication atropine is the antidote.

L8 ANSWER 2 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB Objective: To review the drug treatment of Alzheimer's disease (AD) and to provide guidelines for the physician on how to integrate these treatments into the overall management of this **disorder**. Method: A qualitative review of randomized, double-blind, placebo-controlled trials of medications used to treat **cognitive** deficits, disease progression, agitation, psychosis, or depression in AD. A computerized search of Medline was used to identify relevant literature published during the period 1968-1998. Key words used in the search were 'randomized controlled trials,' with 'dementia' and with 'Alzheimer's disease'. Results: Agents that are currently available in Canada to treat the **cognitive** deficits of AD include **donepezil**, ginkgo biloba, selegiline, and ergoloid mesylates. **Donepezil** and ginkgo biloba are associated with a statistically significant but clinically modest improvement in **cognitive** function in a substantial minority of patients with mild to moderate AD. Selegiline may have a mild beneficial effect on **cognitive** function in some patients with AD, but the data are inconclusive. Ergoloid mesylates have questionable efficacy in AD and can only be recommended as a last line of treatment. The results of a single trial suggest that vitamin E or selegiline (both have antioxidant properties) may slow the progression of AD. Antipsychotic medications can result in clinically significant improvement in agitation and psychosis. Carbamazepine also appears to be an effective treatment for agitation in AD, and there is preliminary evidence that the selective serotonin reuptake inhibitor citalopram reduces irritability in this **disorder**. There is no evidence that other nonneuroleptic medications are more efficacious than placebo in treating agitation in AD. Limited data indicate that depression in dementia responds to antidepressant medication. Conclusion: These data indicate that selected medications can be used to treat **cognitive** deficits, disease progression, agitation, psychosis, and depression in AD. However, there is considerable heterogeneity in patients' responses to these medications. Pharmacotherapy needs to be considered as a component of a package of care that also includes psychosocial and environmental interventions and support of the caregiver.

L8 ANSWER 3 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB Alzheimer's disease is a chronic neurodegenerative **disorder** that is characterized by memory impairment, **cognitive** dysfunction, behavioral disturbances, and deficits in activities of daily living. A consistent observation in these patients is that cholinergic neurons are affected and deteriorate over time, leading to decreased levels of acetylcholine (ACh). Acetylcholinesterase (ACHE) inhibitors, which attempt to prevent the breakdown of ACh, may be classified as short acting, intermediate acting, and long acting based on AChE regeneration time. **Metrifonate** is converted by a nonenzymatic process to the long-acting cholinesterase inhibitor 2,2- dichlorovinyl dimethyl phosphate (DDVP). Acetylcholinesterase inhibition produced by **metrifonate** occurs rapidly, is dose dependent, can be detected by inhibition measured in red blood cells, and can be reversed by oxime administration. **Metrifonate** and DDVP improved performance in young rats; **cognitive** improvement in aged rats also was observed. Both agents were well tolerated and did not have significant effects on various preclinical pharmacologic safety tests.

L8 ANSWER 4 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB Alzheimer's disease is a degenerative **disorder** of the central nervous system with unknown origin, and polymorphic symptomatology. Many details of its aetiopathogenesis have been clarified and different therapeutic strategies have been based on these results in the last decades. After the outline of the current diagnostics of the disease, the possible therapeutic strategies of **cognitive** and non-

cognitive symptoms are summarised. Usage of the different acetylcholinesterase inhibitors (tacrin, **donepezil**, etc.) are in the foreground presently. Recently slowing of progression was verified using different neuroprotective agents, such as selegiline and Vitamin E, and different further data are available in the frame of other models (e.g. infective or vascular models). In Hungary the association of Alzheimer's disease and vascular dementia is very frequent; nootrop drugs seem to be very important in the slight and moderate stages of the disease. Non-**cognitive** symptoms are very frequent, making a great burden for the caregivers. Even the available drugs can be used with success. Favourable results of cholinergic strategies seem to be promising, like in a recently finished study with xanomeline. Evaluation of the effect of new drugs is based on internationally accepted strict standards. Planning the complex therapy for a longer period is favoured, considering the possibilities of psychological and sociological approaches, which are also discussed in the different stages of Alzheimer's disease.

L8 ANSWER 5 OF 5 SCISEARCH COPYRIGHT 2003 THOMSON ISI

AB BACKGROUND-Alzheimer's disease (AD) is a progressive dementia associated with distinct neuropathologic changes and characterized by memory loss and impairment in at least one other area of cognition. The underlying neuropathologic substrate for **cognitive** and noncognitive behavioral disturbances in AD is uncertain, but likely includes deficiencies of cholinergic and other transmitters in addition to plaques and tangles.

REVIEW-Therapies based on cholinergic hypotheses have lead to two approved drugs, tacrine and **donepezil**; other cholinergic drugs, including cholinesterase inhibitors, muscarinic agonists, and nicotinic agonists, are under development. Other therapies have been devised based on presumed risk and protective factors, such as aging, APO E genotype, head trauma, menopause/estrogen deficiency, the effect of education on the brain, anti-inflammatory drugs, and antioxidants. Recently, numerous basic studies have demonstrated the significance of amyloid protein, tau protein, and apolipoprotein E in the pathogenesis of plaques and tangles.

SUMMARY-Treatment of the **cognitive** disturbances in AD will likely use multiple approaches to improve symptoms and to slow progression. Therapy for the noncognitive disturbances involves communication between the clinician and the caregiver, as well as pharmacologic and nonpharmacologic treatments.

CONCLUSIONS-AD is a heterogeneous **disorder**. Treatment must be individualized and must address both **cognitive** and noncognitive disturbances. Future therapies may also take various genetic risk factors and gender into account.

=> d l8 2 bib,ab

L8 ANSWER 2 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 1998388110 EMBASE

TI The pharmacologic treatment of Alzheimer's disease: A guide for the general psychiatrist.

AU Flint A.J.; Van Reekum R.

CS Dr. A.J. Flint, Toronto Hospital, General Division, 200 Elizabeth Street, Toronto, Ont. M5G 2C4, Canada. aflint@torhosp.toronto.on.ca

SO Canadian Journal of Psychiatry, (**1998**) 43/7 (689-697).
Refs: 56
ISSN: 0706-7437 CODEN: CJPSDF

CY Canada

DT Journal; General Review

FS 008 Neurology and Neurosurgery
020 Gerontology and Geriatrics
032 Psychiatry
037 Drug Literature Index

038 Adverse Reactions Titles
LA English
SL English; French
AB Objective: To review the drug treatment of Alzheimer's disease (AD) and to provide guidelines for the physician on how to integrate these treatments into the overall management of this **disorder**. Method: A qualitative review of randomized, double-blind, placebo-controlled trials of medications used to treat **cognitive** deficits, disease progression, agitation, psychosis, or depression in AD. A computerized search of Medline was used to identify relevant literature published during the period 1968-1998. Key words used in the search were 'randomized controlled trials,' with 'dementia' and with 'Alzheimer's disease'. Results: Agents that are currently available in Canada to treat the **cognitive** deficits of AD include **donepezil**, ginkgo biloba, selegiline, and ergoloid mesylates. **Donepezil** and ginkgo biloba are associated with a statistically significant but clinically modest improvement in **cognitive** function in a substantial minority of patients with mild to moderate AD. Selegiline may have a mild beneficial effect on **cognitive** function in some patients with AD, but the data are inconclusive. Ergoloid mesylates have questionable efficacy in AD and can only be recommended as a last line of treatment. The results of a single trial suggest that vitamin E or selegiline (both have antioxidant properties) may slow the progression of AD. Antipsychotic medications can result in clinically significant improvement in agitation and psychosis. Carbamazepine also appears to be an effective treatment for agitation in AD, and there is preliminary evidence that the selective serotonin reuptake inhibitor citalopram reduces irritability in this **disorder**. There is no evidence that other nonneuroleptic medications are more efficacious than placebo in treating agitation in AD. Limited data indicate that depression in dementia responds to antidepressant medication. Conclusion: These data indicate that selected medications can be used to treat **cognitive** deficits, disease progression, agitation, psychosis, and depression in AD. However, there is considerable heterogeneity in patients' responses to these medications. Pharmacotherapy needs to be considered as a component of a package of care that also includes psychosocial and environmental interventions and support of the caregiver.

L8 ANSWER 2 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1998388110 EMBASE
TI The pharmacologic treatment of Alzheimer's disease: A guide for the general psychiatrist.
AU Flint A.J.; Van Reekum R.
CS Dr. A.J. Flint, Toronto Hospital, General Division, 200 Elizabeth Street, Toronto, Ont. M5G 2C4, Canada. aflint@torhosp.toronto.on.ca
SO Canadian Journal of Psychiatry, (**1998**) 43/7 (689-697).
Refs: 56
ISSN: 0706-7437 CODEN: CJPSDF
CY Canada
DT Journal; General Review
FS 008 Neurology and Neurosurgery
020 Gerontology and Geriatrics
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English; French
AB Objective: To review the drug treatment of Alzheimer's disease (AD) and to provide guidelines for the physician on how to integrate these treatments into the overall management of this **disorder**. Method: A qualitative review of randomized, double-blind, placebo-controlled trials of medications used to treat **cognitive** deficits, disease progression, agitation, psychosis, or depression in AD. A computerized search of Medline was used to identify relevant literature published during the period 1968-1998. Key words used in the search were 'randomized controlled trials,' with 'dementia' and with 'Alzheimer's disease'. Results: Agents that are currently available in Canada to treat the **cognitive** deficits of AD include **donepezil**, ginkgo biloba, selegiline, and ergoloid mesylates. **Donepezil** and ginkgo biloba are associated with a statistically significant but clinically modest improvement in **cognitive** function in a substantial minority of patients with mild to moderate AD. Selegiline may have a mild beneficial effect on **cognitive** function in some patients with AD, but the data are inconclusive. Ergoloid mesylates have questionable efficacy in AD and can only be recommended as a last line of treatment. The results of a single trial suggest that vitamin E or selegiline (both have antioxidant properties) may slow the progression of AD. Antipsychotic medications can result in clinically significant improvement in agitation and psychosis. Carbamazepine also appears to be an effective treatment for agitation in AD, and there is preliminary evidence that the selective serotonin reuptake inhibitor citalopram reduces irritability in this **disorder**. There is no evidence that other nonneuroleptic medications are more efficacious than placebo in treating agitation in AD. Limited data indicate that depression in dementia responds to antidepressant medication. Conclusion: These data indicate that selected medications can be used to treat **cognitive** deficits, disease progression, agitation, psychosis, and depression in AD. However, there is considerable heterogeneity in patients' responses to these medications. Pharmacotherapy needs to be considered as a component of a package of care that also includes psychosocial and environmental interventions and support of the caregiver.

=>

L2 ANSWER 1 OF 1 USPATFULL
AN 2000:150180 USPATFULL
TI Substituted 4-oxo-napthyridine-3-carboxamides: GABA brain receptor ligands
IN Albaugh, Pamela A., Clinton, CT, United States
DeSimone, Robert W., Durham, CT, United States
Liu, Gang, Agoura, CA, United States
PA Neurogen Corporation, Branford, CT, United States (U.S. corporation)
PI US 6143760 20001107 <--
AI US 1998-139456 19980825 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Seaman, D. Margaret
LREP McDonnell Boenn Hulbert & Berghoff, Sarussi, Steven J.
CLMN Number of Claims: 110
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6143760 20001107 <--
IT 220860-38-8P 220860-41-3P 220860-42-4P 220860-43-5P 220860-44-6P
220860-45-7P 220860-46-8P 220860-47-9P 220860-48-0P 220860-49-1P
220860-50-4P 220860-51-5P 220860-53-7P 220860-54-8P 220860-55-9P
220860-56-0P 220860-57-1P 220860-58-2P 220860-59-3P 220860-60-6P
220860-61-7P 220860-62-8P 220860-63-9P 220860-64-0P 220860-65-1P
220860-66-2P 220860-67-3P 220860-68-4P 220860-69-5P 220860-70-8P
220860-71-9P 220860-72-0P 220860-73-1P 220860-74-2P 220860-75-3P
220860-76-4P 220860-77-5P 220860-78-6P 220860-79-7P 220860-80-0P
220860-81-1P 220860-82-2P 220860-83-3P 220860-84-4P 220860-85-5P
220860-86-6P 220860-87-7P 220860-88-8P 220860-89-9P 220860-91-3P
220860-92-4P 220860-93-5P 220860-94-6P 220860-95-7P
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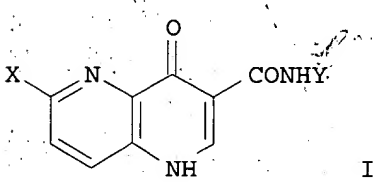
220861-03-0P 220861-08-5P 220861-09-6P 220861-10-9P 220861-11-0P
220861-13-2P 220861-14-3P 220861-15-4P 220861-16-5P 220861-19-8P
220861-21-2P 220861-22-3P 220861-25-6P 220861-26-7P 304680-78-2P
304680-79-3P 304680-80-6P 304680-81-7P 304680-82-8P 304680-83-9P
304680-84-0P 304680-85-1P 304680-86-2P 304680-87-3P 304680-88-4P
304680-89-5P 304680-90-8P 304680-91-9P 304680-92-0P 304680-93-1P
304680-94-2P 304680-95-3P 304680-96-4P 304680-97-5P 304680-98-6P
(prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as agonists, antagonists or inverse agonists for GABAa brain receptors)

AN 133:335225 CA
TI Substituted 4-oxo-naphthyridine-3-carboxamides: GABA brain receptor ligands
IN Albaugh, Pamela A.; Desimone, Robert W.; Liu, Gang
PA Neurogen Corp., USA
SO U.S., 27 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-44
ICS C07D471-02
NCL 514300000
CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6143760	A	20001107	US 1998-139456	19980825
	ZA 9807957	A	20000322	ZA 1998-7957	19980901
	US 6399604	B1	20020604	US 2000-634093	20000808
	US 2002156280	A1	20021024	US 2002-114743	20020402
PRAI	US 1997-56799P	19970825			
	US 1998-139456	19980825			
	US 2000-634093	20000808			

GI



I

AB The present invention encompasses substituted 4-oxo-naphthyridine-3-carboxamides I or the pharmaceutically acceptable nontoxic salts of I (X = H, halogen, (un)substituted alkyl, (un)substituted alkoxy or amino; and Y is (un)substituted alkyl, aryl, or heteroaryl). I are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. I are useful in the diagnosis and treatment of anxiety, Down Syndrome, sleep, cognitive and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness.

ST oxonaphthyridinecarboxamide prepn GABA brain receptor ligand

IT GABA agonists
GABA antagonists
(GABAA; prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as GABA brain receptor ligands)

IT Sleep
(disorder; prepn. of substituted 4-oxo-naphthyridine-3-carboxamides in treatment of)

IT Amides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(naphthyridine-3-carboxamides; prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as GABA brain receptor ligands)

IT Anxiety
Down's syndrome
Seizures
(prepn. of substituted 4-oxo-naphthyridine-3-carboxamides in treatment

of)
IT 100961-91-9P
RL: BYP (Byproduct); PREP (Preparation)
(formation in prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as agonists, antagonists or inverse agonists for GABAa brain receptors)
IT 220860-38-8P 220860-41-3P 220860-42-4P 220860-43-5P 220860-44-6P
220860-45-7P 220860-46-8P 220860-47-9P 220860-48-0P 220860-49-1P
220860-50-4P 220860-51-5P 220860-53-7P 220860-54-8P 220860-55-9P
220860-56-0P 220860-57-1P 220860-58-2P 220860-59-3P 220860-60-6P
220860-61-7P 220860-62-8P 220860-63-9P 220860-64-0P 220860-65-1P
220860-66-2P 220860-67-3P 220860-68-4P 220860-69-5P 220860-70-8P
220860-71-9P 220860-72-0P 220860-73-1P 220860-74-2P 220860-75-3P
220860-76-4P 220860-77-5P 220860-78-6P 220860-79-7P 220860-80-0P
220860-81-1P 220860-82-2P 220860-83-3P 220860-84-4P 220860-85-5P
220860-86-6P 220860-87-7P 220860-88-8P 220860-89-9P 220860-91-3P
220860-92-4P 220860-93-5P 220860-94-6P 220860-95-7P 220860-98-0P
220860-99-1P 220861-00-7P 220861-01-8P 220861-02-9P 220861-03-0P
220861-08-5P 220861-09-6P 220861-10-9P 220861-11-0P 220861-13-2P
220861-14-3P 220861-15-4P 220861-16-5P 220861-19-8P 220861-21-2P
220861-22-3P 220861-25-6P 220861-26-7P 304680-78-2P 304680-79-3P
304680-80-6P 304680-81-7P 304680-82-8P 304680-83-9P 304680-84-0P
304680-85-1P 304680-86-2P 304680-87-3P 304680-88-4P 304680-89-5P
304680-90-8P 304680-91-9P 304680-92-0P 304680-93-1P 304680-94-2P
304680-95-3P 304680-96-4P 304680-97-5P 304680-98-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as agonists, antagonists or inverse agonists for GABAa brain receptors)
IT 64-17-5, Ethanol, reactions 87-13-8, Diethyl ethoxymethylenemalonate
100-46-9, Benzylamine, reactions 109-73-9, Butylamine, reactions
4548-45-2, 2-Chloro-5-nitropyridine 17201-43-3,
.alpha.-Bromo-p-tolunitrile 24424-99-5, Di-tert-butyl dicarbonate
54303-30-9, 2-(Ethylthio)ethylamine hydrochloride 220861-33-6
220861-34-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as agonists, antagonists or inverse agonists for GABAa brain receptors)
IT 2393-23-9P, 4-Methoxybenzylamine 21626-41-5P,
2-Benzylamino-5-nitropyridine 21630-48-8P 31594-45-3P,
2-Ethoxy-5-nitropyridine 34403-48-0P 52025-34-0P,
2-Ethoxy-5-aminopyridine 92808-09-8P 92808-14-5P 92808-33-8P
220861-28-9P 220861-29-0P 220861-31-4P 304680-99-7P 304681-00-3P
304681-01-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(reactant for prepn. of substituted 4-oxo-naphthyridine-3-carboxamides as agonists, antagonists or inverse agonists for GABAa brain receptors)
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
(1) Anon; DE 2322750 1973 CAPLUS
(2) Anon; DE 2407744 1974 CAPLUS
(3) Anon; DE 279875 A1 1990
(4) Anon; DE 279887 A1 1990
(5) Anon; DE 295360 A5 1991
(6) Geoffrey, W; Molecular Neuroscience, NeuroReport 1995, V6, P1313
(7) Haskell; US 4374138 1983 CAPLUS
(8) Heindl, J; Eur J Med Chem 1977, V6, P549
(9) Kondo, K; Patent Abstracts of Japan 1999, V13(260)
(10) Laruelle; US 4621088 1986 CAPLUS
(11) Murakami; US 3953428 1976 CAPLUS
(12) Nuebling; US 5378679 1995 CAPLUS
(13) White, G; Receptors and Channels 1995, V3, P1 CAPLUS

L5 ANSWER 1 OF 1 USPATFULL
AN 2000:150180 USPATFULL
TI Substituted 4-oxo-napthyridine-3-carboxamides: GABA brain receptor ligands
IN Albaugh, Pamela A., Clinton, CT, United States
DeSimone, Robert W., Durham, CT, United States
Liu, Gang, Agoura, CA, United States
PA Neurogen Corporation, Branford, CT, United States (U.S. corporation)
PI US 6143760 20001107 <--
AI US 1998-139456 19980825 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Seaman, D. Margaret
LREP McDonnell Boenn Hulbert & Berghoff, Sarussi, Steven J.
CLMN Number of Claims: 110
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6143760 20001107 <--
DETD (v) N-**Benzyl** 6-**methoxy**-4-**oxo**-1,4-**tetrahydro**-1,5-**naphthyridine**-3-**carboxamide**; (Compound 33) m.p. 273-274.degree. C.
DETD (yyy) N-**Benzyl** 6-(2-**methoxy**)ethylamino-4-**oxo**-1,4-**tetrahydro**-1,5-**naphthyridine**-3-**carboxamide**; (Compound 84) m.p.254-257.degree. C.
CLM What is claimed is:
38. A compound according to claim 1, which is N-**Benzyl** 6-**methoxy**-4-**oxo**-1,4-**tetrahydro**-1,5-**naphthyridine**-3-**carboxamide**.

91. A compound according to claim 1, which is N-**Benzyl** 6-(2-**methoxy**)ethylamino-4-**oxo**-1,4-**tetrahydro**-1,5-**naphthyridine**-3-**carboxamide**.